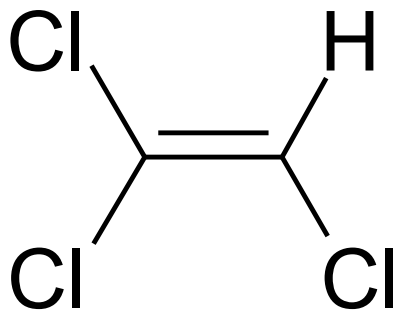
United States Environmental Protection Agency
Office of Chemical Safety and Pollution Prevention

TSCA Workplan Chemical Risk Assessment for Trichloroethylene:

Degreaser and Arts/Crafts Uses

CASRN: 79-01-6

Ethene, 1,1,2-trichloro-



December 2012

NOTICE

This document is an **External Review Draft**. This information is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by EPA. It does not represent and should not be construed to represent any Agency determination or policy. It is being circulated for review of its technical accuracy and science policy implications.

Table of Contents

AUTHORS / CONTRIBUTORS / ACKNOWLEDGEMENTS / REVIEWERS 6

GLOSSARY OF TERMS AND ABBREVIATIONS 7

EXECUTIVE SUMMARY 10

CHAPTER 1: BACKGROUND AND SCOPE 13

BACKGROUND 13
SCOPE OF ASSESSMENT FOR TCE 14

CHAPTER 2: SOURCES AND ENVIRONMENTAL FATE OF TCE 17

A. PHYSICAL AND CHEMICAL PROPERTIES OF TCE 17
B. ENVIRONMENTAL FATE 18
C. PRODUCTION VOLUME AND GENERAL INFORMATION ON USES 22

CHAPTER 3: HUMAN HEALTH RISK ASSESSMENT 23

A. ENVIRONMENTAL RELEASES AND EXPOSURE SUMMARY 23
ENVIRONMENTAL RELEASES OF TCE 23
Calculating Exposures used in this Risk Assessment 30
Consumer Exposures – Degreaser and Arts/Crafts Uses of TCE 31
B. HAZARD SUMMARY 34
Toxicokinetics (Absorption, Distribution, Metabolism, and Excretion) 35
Summary of Toxicity Information on TCE 39
Hazard Data to be used in Risk Assessment for TCE 56
C. HUMAN HEALTH RISK CHARACTERIZATION 58
Risk Estimation Approach for Acute and Repeated Exposures 58
Risk Estimates for Acute (Short-Term) and Chronic (Repeated) Exposures to TCE 61
Summary 66
D. DISCUSSION OF KEY SOURCES OF UNCERTAINTY AND DATA LIMITATIONS 70
Uncertainties in the Exposure Assessment 70
Uncertainties in the Hazard Assessment 71
Uncertainties in the Risk Assessment 72
CONCLUSIONS 73

REFERENCES 74

APPENDIX A: REGULATORY HISTORY OF TCE AT THE US EPA 87

APPENDIX B: 2006 INVENTORY UPDATE RULE DATA FOR TCE 89

APPENDIX C: NAICS CODES FOR TCE DEGREASING 92

APPENDIX D: CALCULATIONS FOR SMALL COMMERCIAL WORKER DEGREASER EXPOSURES 94

APPENDIX E: CONVERTING E-FAST ADRS TO CONCENTRATION IN AIR 98

APPENDIX F: HAZARD VALUES IDENTIFIED FOR USE IN THIS RISK ASSESSMENT 100

List of Tables

Table 1-1. Primary Uses of TCE and Determination of Inclusion in this Risk Assessment. 15

Table 2-1. Physical-Chemical Properties of TCE[a] 17

Table 2-2. Environmental Fate Characteristics of TCE[a]. 21

Table 3-1. TCE Ambient Air Monitoring Data (µg/m^3)[a]. 24

Table 3-2. The Number of TCE-Emitting Emission Points and Corresponding Total Annual Air Emissions of TCE as reported in the 2008 NEI (US EPA, 2008b). 26

Table 3-3. Total Annual Air Emissions of TCE as Reported in the 2008 TRI (TRI, 2012b). 26

Table 3-4. Relevant TCE Releases from Solvent Cleaning in 2010. 27

Table 3-5. Breakdown of Degreasing Cleaning Machine Type for Point Source TCE Emissions 28

Table 3-6. Estimate of 2010 TCE Releases for Small Industrial/Commercial Facilities (n = 1,483). 29

Table 3-7. Potential Operating TCE Emission Factors from Degreasing (Calculated and Reported Values). 30

Table 3-8. Summary of Potential Workplace TCE Inhalation Exposures: Small Commercial Degreaser. .. 31

Table 3-9. TCE Products in Household Products Database Retrieval 32

Table 3-10. Estimated TCE Potential Acute Dose Rates from Use of Two Hobbyist Products Indoors at Residences as Determined by E-FAST. 33

Table 3-11. Estimated TCE Inhalation Calculated Concentration in Air (Over the Course of a Day[a]) from Use of Two Hobbyist Products Indoors at Residences 34

Table 3-12. Hazard/Risk Assessment Documents Consulted for this Report. 34

Table 3-13. Common Metabolites of TCE and Related Compounds[a] 36

Table 3-14. TCE Metabolites Identified by Pathway[a] 37

Table 3-15: Half-Life Data For TCE in Rats and Humans[a]. 39

Table 3-16. Proposed AEGL Values for TCE (in ppm)[a]. 41

Table 3-17. Inhalation Studies Identified In US EPA (2011c) For Use In OPPT TCE Risk Assessment. 54

Table 3-18. U.S. EPA IRIS PBPK-Modeled Dose Metrics for TCE Dose-Response Assessment. 57

Table 3-19. Range of TCE Candidate POD/HEC Values Derived by US EPA (2011c). 58

Table 3-20. Use Scenarios, Population of Concern, and Health Effects of Concern. 60

Table 3-21. TCE Noncancer Risk Estimates for Small Commercial Degreasers and Non-users: Using the Lowest 99th Percentile HECs (Numbers are MOEs)[1,2] 63

Table 3-22. TCE Cancer Risk Estimates for Small Commercial Degreasers and Non-users (Numbers are Extra Lifetime Cancer Risk and Bolded Vales Represent Concern 64

Table 3-23. TCE Non-cancer Risk Estimates for Use of Two Hobbyist Products Indoors at Residences: Neurotoxicity as Endpoint of Concern and Using the Lowest 99th Percentile HECs and 24-Hour Average Exposure Concentrations (Numbers are MOEs])[1] 65

Table 3-24. TCE Non-cancer Risk Estimates for Use of Two Hobbyist Products Indoors at Residences: Developmental Toxicity as Endpoint of Concern Using the Lowest 99th Percentile HECs and 24-Hour Average Exposure Concentrations (Numbers are MOEs)[1] 66

Table 3-25. Summary of Overall Risk Assessment for TCE Using the Lowest 99th Percentile HECs 67

Table 3-26. Changes in the Non-Cancer MOEs If Different HECs are Used [a] 69

Table B-1. US EPA 2006 IUR Data for TCE. 89

Table B-2. National Chemical Information. 90

Table B-3. Summary of TCE Uses. 90

Table B-4. TCE Use Category Summary. 91

Table C-1. TCE Used as a Degreaser Primarily in These Industries (US Census, 2008). 92

Table D-1. Near-Field/Far-Field Model Inputs. 96

Table D-2. Potential Workplace TCE Inhalation Exposures and Number of Workers Exposed; No LEV. 96

Table D-3. Potential Workplace TCE Inhalation Exposures and Number of Workers Exposed; With LEV. 97

Table E-1. Estimated TCE Inhalation Calculated Concentration in Air (Over Course of Day) from Use of Two Hobbyist Products Indoors at Residences. 99

Table F-1. Studies Identified In US EPA (2011c) For Use In Dose-Response Assessment For TCE. 100

List of Figures

Figure D-1. An Illustration of an Imperfectly Mixed Room; Near-Field/Far-Field Approximation of a Solvent Cleaning Facility; Potential Worker Exposures Depend on How Close a Worker is to the Emission (Volatile) Source. 94

Authors / Contributors / Acknowledgements / Reviewers

This report was developed by the Office of Pollution Prevention and Toxics (OPPT), Office of Chemical Safety and Pollution Prevention (OCSPP). The 2012 workplan risk assessments were prepared based on existing data and any additional information received up to June 15, 2012. Mention of trade names does not constitute endorsement by the US EPA.

EPA Assessment Team

Lead: Louis Scarano, OPPT/RAD

Team: David Lynch, OPPT/EETD Lead
Marcus Aguilar, OPPT/CCD
Rehan Choudhary, OPPT/EETD
Lynn Delpire, OPPT/EETD (retired)
Cathy Fehrenbacher, OPPT/EETD
Kathy Hart, OPPT/EETD
Laura Nielsen, OPPT/EETD
Nhan Nguyen, OPPT/EETD
Justin Roberts, OPPT/EETD
Yvette M. Selby – Mohamadu, OPPT/EETD
David Tobias, OPPT/EETD

Acknowledgements

Weihsueh Chiu, ORD/NCEA for consultations on TCE IRIS assessment and PBPK modeling

Acknowledgements

Portions of this document were developed with support from:

Contractor name	(contract number)	Task
SRC, Inc.	(EP-W-12-003)	Environmental Fate

Internal Peer Reviewers

H. Kay Austin, OPPT/EETD
Stan Barone Jr., OPPT/RAD
Todd Stedeford, OPPT/RAD

External Peer Review - A peer review panel is being arranged for this influential workplan assessment product based upon need and following Agency peer review guidance. The format will be a teleconference of an *ad hoc* panel meeting consisting of independent experts.

Glossary of Terms and Abbreviations

µg/m^3	Microgram(s) per cubic meter
ACGIH	American Conference of Governmental Industrial Hygienists
ADR	Acute dose rate
AEGL	Acute Exposure Guideline Level
ATSDR	Agency for Toxic Substances and Disease Registry
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
BMD	Benchmark dose
BMDL	Benchmark dose, lower confidence limit(s)
BOD	Biochemical oxygen demand
CalEPA	California Environmental Protection Agency
CASRN	Chemical Abstracts Service Registry Number
CCD	Chemical Control Division
CEM	Consumer Exposure Module
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CI	Confidence interval
CNS	Central nervous system
cRfC	Candidate reference concentration
CYP	Cytochrome P450
DCA	Dichloroacetic acid
DCAC	Dichloroacetyl chloride
DCVC	S-Dichlorovinyl-L-cysteine (collectively, the 1,2- and 2,2- isomers)
DCVG	S-Dichlorovinyl-glutathione
DCVT	Dichlorovinyl thiol
DIY	Do-it-yourself
DNA	Deoxyribonucleic acid
ECA	Enforceable consent agreement
EEG	Electroencephalogram
EETD	Economics, Exposure and Technology Division
E-FAST	Exposure and Fate Assessment Screening Tool
EFH	Exposure Factors Handbook
EIS	Emissions Inventory System
EU	European Union
g	Gram(s)
GGTP	Gamma glutamyl transpeptidase
GSH	Glutathione (reduced)
HAP	Hazardous air pollutant
HCV	Human cancer value
HEC	Human equivalent concentration
HEC_{50}	“Typical” human equivalent concentration
HEC_{99}	“Sensitive” human equivalent concentration

HSIA	Halogenated Solvents Industry Alliance, Inc.
lb	Pound(s)
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
IUR	Inhalation unit risk
kg	Kilogram(s)
LADC	Lifetime average daily concentration
LADD	Lifetime average daily dose
LEV	Local exhaust ventilation
LOAEL	Lowest-observed-adverse-effect level
MCL	Maximum contaminant level
MCLG	Maximum contaminant level goal
mg/kg-bw/day	Milligram(s) per kilogram body weight per day
mg/L	Milligram(s) per liter
mg/m^3	Milligram(s) per cubic meter
mg/mL	Milligram(s) per milliliter
MITI	Ministry of International Trade and Industry
MOE	Margin of Exposure
MOE_{acute}	Margin of Exposure (for acute exposure/hazard concerns)
$MOE_{chronic}$	Margin of Exposure (for chronic exposure/hazard concerns)
MOU	Memorandum of understanding
NAcDCVC	N-Acetyl-S-(1,2-dichlorovinyl)-L-cysteine
NAICS	North American Industry Classification System
NAS	National Academy of Sciences
NCI	National Cancer Institute
NEI	National Emissions Inventory
NHL	Non-Hodgkins lymphoma
NIH	National Institutes of Health
NOAEL	No-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NIOSH	National Institute for Occupational Safety and Health
NPL	National Priority List
NTP	National Toxicology Program
OAR	Office of Air and Radiation
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organisation for Economic Co-operation and Development
OPPT	Office of Pollution Prevention and Toxics
OR	Odds ratio
OSHA	Occupational Safety and Health Administration
OSWER	Office of Solid Waste and Emergency Response
OW	Office of Water
PBPK	Physiologically-based pharmacokinetic
p-cRFCs	PBPK model-based candidate RfCs
PFC	Plaque-forming cell

PND	Postnatal day
POD	Point of departure
POTW	Publicly owned treatment works
ppb	Parts per billion
ppm	Parts per million
PVC	Polyvinyl chloride
RAD	Risk Assessment Division
RCC	Renal cell carcinoma
RCRA	Resource Conservation and Recovery Act
RfC	Reference concentration
RfD	Reference dose
RR	Rate ratio
RRm	Summary relative risk
SAB	Science Advisory Board
SARA	Superfund Amendments and Reauthorization Act
SCC	Source Classification Code
TCA	Trichloroacetic acid
TCE	Trichloroethylene
TCOG	Trichloroethanol, glucuronide conjugate
TCOH	Trichloroethanol
TRI	Toxics Release Inventory
TTC	Total trichloro compounds
TSCA	Toxic Substances Control Act
TWA	Time-weighted average
UF	Uncertainty factor
US	United States
US EPA	United States Environmental Protection Agency
VCCEP	Voluntary Children's Chemical Evaluation Program
VOC	Volatile organic compound

Executive Summary

Trichloroethylene (TCE) was identified for risk assessment as part of the United States (US) Environmental Protection Agency's (EPA)'s Existing Chemicals Management Program. The US EPA reviewed readily available information on TCE including uses, physical and chemistry properties, fate, exposure potential, and associated hazards to humans and the environment.

TCE was selected based on concerns for its human health hazard (*e.g.,* probable human carcinogen), and its exposure profile (*i.e.,* widely used in consumer products and detected in drinking water, indoor environments, surface water, ambient air, groundwater, and soil) using the recently adopted Office of Pollution Prevention and Toxics (OPPT) screening methodology (US EPA, 2012c). TCE also was determined to have moderate persistence and low bioaccumulation potential. The potential for environmental effects was judged to be low because of TCE's moderate persistence, low bioaccumulation, and low hazard for aquatic toxicity. This risk assessment does not include an assessment of environmental effects.

TCE is a volatile organic compound (VOC) that is produced or imported into the US in large quantities (>250 million lbs (lbs) per year) and has multiple uses. The majority, roughly 84 percent, of TCE is used as an intermediate chemical for manufacturing refrigerant chemicals, but no emission information was available because it is processed in a closed system. Much of the remaining ~15 percent is used as a solvent for metals degreasing, leaving a relatively small percentage to account for all other uses, including its use in consumer products.

This assessment is focused on TCE's use as a degreaser in small commercial settings[1] and by consumers in residential settings and its use as a clear protective coating spray by arts and crafts hobbyists. Due to TCE's high volatility, all exposures were evaluated for the inhalation exposure pathway only. The US EPA recognizes that dermal exposure can occur, but this exposure pathway is considered less significant and was not considered within the scope of this risk assessment.

For the exposure assessment, OPPT reviewed available data from three separate sources (*i.e.,* National Emissions Inventory [NEI], Toxics Release Inventory [TRI], and the North American Industry Classification System [NAICS]) and developed estimates for exposures for the small commercial degreaser use. There were no reliable data regarding the hobbyist scenarios, so OPPT estimated hobbyist exposures using a standard exposure assessment modeling approach (*i.e.,* EPA's Exposure and Fate Assessment Screening Tool [E-FAST], Consumer Exposure Module [CEM]).

Modeling and evaluation were used to develop exposure estimates for the following exposure scenarios: small commercial degreaser worker; consumer/hobbyist degreaser user; and consumer/hobbyist clear protective coating spray user. For all three scenarios, exposure estimates also were developed for bystanders (*i.e.,* non-users) defined as individuals not actually using the TCE product, but who are physically nearby and thus, possibly exposed.

[1] Small commercial settings represent small businesses that use degreaser products/equipment regularly, but not all day during the course of their job. An example would be a garage/car mechanic business.

For the hazard information, the US EPA relied on the Integrated Risk Information System's (IRIS) published toxicological review of TCE (US EPA, 2011c). This information was used to identify non-cancer hazard values for acute (*i.e.,* single or short-term) and chronic (*i.e.,* repeated) exposure conditions. There were 27 different candidate studies identified that evaluated 32 endpoints, which encompassed a variety of effects following both acute (*i.e.,* developmental toxicity and neurotoxicity) and chronic (*i.e.,* liver, kidney, immunotoxicity, and male reproductive toxicity) exposures. From this pool of studies, OPPT chose 12 studies that used inhalation as the route of exposure. These 12 studies evaluated 17 different endpoints. Hazard values were chosen to represent effects in each of the major target organs. By not limiting the analysis to a single, sensitive endpoint or effect, this assessment allows both the exposure duration and the population exposed to help determine which hazard value may be the most appropriate or important. Other approaches, including use of the IRIS RfC, may be appropriate for other risk assessments.

The IRIS inhalation unit risk (IUR) value, based on concerns for human cancers of the kidney, liver, and non-Hodgkin's lymphoma (NHL), was used for OPPT's TCE cancer risk assessment.

Adult male and female workers and bystanders in small commercial facilities were identified as a population or life stage targeted for chronic or daily exposure scenarios in this assessment. Because acute exposures also can occur during daily exposures, there may be a potential hazard for both neurotoxicity and developmental toxicity; thus, given the latter, women of child-bearing age were included as a life stage or population.

For both the residential consumer and hobbyist user scenarios, the same populations identified for the small commercial worker and bystander scenarios (*i.e.,* males and females, including women of child-bearing age) were used. However, the non-cancer evaluation was limited to acute exposures and to neurological effects to males and females, and developmental effects to women of child-bearing age. For the consumer, non-user population, the US EPA identified all ages for evaluation because all-age members of a household could be in the home during the use of the consumer product.

For all non-cancer risk calculations, the Margin of Exposure (MOE) approach was used. In this approach, the hazard value is divided by the exposure value to derive a number that is compared to conventional benchmark values used to estimate or quantify risk. In this risk assessment, all of the hazard values were derived using a special mathematical model as determined by US EPA (2011c). The modeling exercise used test data from both animals and humans to derive values called Human Equivalent Concentrations (HEC). Although many HEC values were calculated by the IRIS program, in this assessment a more conservative value was used (*i.e.,* the lower bound 99th percentile HEC value) for each of the non-cancer adverse effect outcomes evaluated.

When the hazard value (HEC) is divided by the exposure value, the resulting number is called the "Margin of Exposure" or MOE. In this risk assessment, if the value is determined as less than 30, there is a potential risk concern; if the value is found as greater than 30, there is no risk concern.

For the cancer risk assessment, a different metric was used to quantify risk. The method EPA used calculated extra cancer risk from benchmarks of concern based on no more than one excess cancer in a population of 100,000 workers (*i.e.,* 1×10^{-5}) or one excess cancer in a population of one million nonworkers (*i.e.,* 1×10^{-6}).

EPA relied on physiologically-based pharmacokinetic (PBPK) modeling performed by the US EPA's IRIS program, which resulted in a variety of hazard values to represent HECs. In choosing the values used, assumptions were made that could introduce some uncertainty into the risk assessment. However, using conservative measures (*i.e.,* the lower bound 99th percentile HEC) and values from inhalation-only studies for each of the six major target organs or adverse effects associated with TCE, strengthens the degree of confidence that the risks were not under-estimated for the scenarios evaluated in this report.

As with any risk assessment, there are uncertainties that need to be considered when interpreting the results. Assumptions were used in estimating the exposure scenarios covered in this assessment. Examples include assumptions about the number and duration of use events (*i.e.*, how often a consumer may use a degreaser or clear protective coating spray product) and the assumptions used to estimate inhalation exposures to small shop commercial degreaser workers. OPPT did not quantify these uncertainties and recognizes that they may under- or over-estimate actual exposure.

Finally, by focusing on six different target organs or effects for chronic and acute exposure durations, rather than on a single, sensitive value or endpoint, the robust hazard database on TCE is fully utilized. This provides important context that is both useful and informative to those interested in understanding the potential risks of concern from TCE exposures for the scenarios evaluated in this risk assessment.

The results of the risk assessment show:

- For the commercial degreaser user and non-user, non-cancer MOEs were less than 30 for acute toxicity for developmental toxicity and neurotoxicity effects, and chronic effects for liver, kidney, and immune system effects. This indicates potential risks of concern.
- For the commercial degreaser user and non-user, using the IRIS IUR the cancer risks were all below the benchmark values. This indicates potential risks of concern.
- For the hobbyist degreaser user and non-user and for the hobbyist clear protective spray users, the acute non-cancer MOEs for developmental toxicity were less than 30. This indicates potential risks of concern.
- The hobbyist clear protective spray non-user scenario resulted in an MOE of greater than 30 for both developmental toxicity and neurotoxicity. This indicates no potential risks of concern.

Chapter 1: Background and Scope

Trichloroethylene (TCE) has been identified for assessment as part of the United States (US) Environmental Protection Agency's (EPA) Existing Chemicals Management Program. TCE was selected based on EPA's concerns for human health hazard (*i.e.,* probable human carcinogen), and its exposure profile (*i.e.,* widely used in consumer products and detected in drinking water, indoor environments, surface water, ambient air, groundwater, and soil) using the recently adopted Office of Pollution Prevention and Toxics (OPPT) screening methodology (US EPA, 2012c).

In this chapter, a brief discussion is presented on the steps that EPA has taken to determine the focus and scope of this risk assessment.

BACKGROUND

TCE is a liquid, volatile organic compound with high vapor pressure, moderate water solubility, and high mobility in soil. The biodegradation of TCE in the environment is dependent on a variety of factors (*e.g.,* pH, resident microorganisms, moisture, *etc.*) and so a wide range of degradation rates are possible, ranging from days to years. TCE also has moderate persistence and low bioaccumulation potential.

This substance is produced or imported into the US in large quantities (*i.e.,* >250 million lbs/ yr) and has many uses. The majority, almost 84 percent, of TCE is used as an intermediate chemical for manufacturing refrigerant chemicals. Much of the remaining roughly 15 percent is used as a solvent for metals degreasing, leaving a relatively small percentage to account for all other uses, including, its use in some consumer products. TCE can be found in consumer products including but not limited to those "do-it-yourself" [DIY] consumer uses such as a solvent for metal degreasing for use on cars, bikes, *etc.*, or as an ingredient in hobbyist products, including a clear protective coating spray for artwork, a film cleaner, a toner aide, and a mirror edge sealant.

Most reported environmental releases of TCE are to air with much fewer releases to landfills and very little releases to water (see Chapter 3, Section A, *Environmental Release and Exposure* Summary).

Due to its high production volume, physical-chemical properties, uses, and environmental releases, TCE has been the subject of various regulations across many offices within the US EPA: the Office of Air and Radiation (OAR), the Office of Solid Waste and Emergency Response (OSWER), the Office of Water (OW), and OPPT. Appendix A provides a review of the US EPA-wide regulatory history of TCE.

The US EPA's assessment of the human health hazard of TCE is largely based on the US EPA's toxicological review of TCE (US EPA, 2011c). This comprehensive review compiled hazard information and was reviewed by the US EPA's Science Advisory Board (SAB) (US EPA, 2011a). In addition, a literature search was conducted in March, 2012 for new information.

SCOPE OF ASSESSMENT FOR TCE

Given that the majority of TCE produced and used in the US is as a chemical intermediate that would not likely result in exposures to the general population, the US EPA assumed that virtually all of the TCE that is used as an intermediate for manufacturing refrigerant chemical is consumed in this process or released as fugitive air emissions. Large-scale manufacturing occupational exposure scenarios were not addressed in this risk assessment. In general, exposures that result from large-scale industrial operations are likely to be better controlled and monitored than those exposures from small commercial settings and consumer uses.

The US EPA focused the assessment on uses of TCE as a degreaser (*i.e.,* both in small commercial settings and by consumers or hobbyists) and on consumer use of TCE in products used by individuals in the arts and crafts field. Bystanders, those who are in the vicinity of the product use, also were addressed. Because of TCE's high volatility, all exposures were evaluated only for the inhalation exposure pathway. The US EPA recognizes that dermal exposure can occur for both of these scenarios, but this exposure pathway is considered less significant and is not considered in this risk assessment.

Information from EPA's toxicological review of TCE (US EPA, 2011c) was used as the basis for developing an assessment of the human health hazard of TCE in targeted use by workers in small commercial degreasing applications and by consumer/hobbyists using TCE as a degreaser and an art spray fixative. EPA identified non-cancer hazard values for acute (*i.e.,* single or short-term) and chronic (*i.e.,* repeated) exposure conditions for a variety of effects including both acute (*i.e.,* developmental toxicity and neurotoxicity) and chronic (*i.e.,* liver, kidney, immunotoxicity, and neurotoxicity) endpoints.

EPA did not evaluate environmental effects in this risk assessment from the manufacture and use of TCE. Available information reviewed in the European Union (EU) risk assessment for TCE (EC, 2004) concluded there were no concerns for environmental effects on aquatic organisms, including benthic organisms, terrestrial organisms, and the atmosphere. The EU risk conclusions were based on the production and use of TCE (*i.e.,* including releases to wastewater treatment plants, to air from all uses, and from dichloroacetic acid [DCA; photodegradation product of TCE]). The hazard information EPA reviewed, particularly the aquatic toxicity data, suggest there is no immediate concern for potential environmental effects.

Table 1-1 shows the use and exposure scenarios considered and the rationale for inclusion or exclusion in this assessment. The primary criteria for inclusion were whether there was a high TCE concentration in the product and the frequency of use of the product. EPA focused its assessment on small commercial operators where workers such as garage mechanics may use a

solvent degreaser at some point as a part of their daily activities. It is assumed that these individuals are all adults (≥16 and older). Furthermore, exposures were estimated and risks were calculated for workers in the vicinity of the degreasing use, but not actually performing the operation (*i.e.*, bystanders).

Table 1-1. Primary Uses of TCE and Determination of Inclusion in this Risk Assessment.

Use Category	Typical Percent TCE Content	Population Exposed	To Be Considered in this Assessment?
Intermediate in the manufacturing of refrigerant	>99	Workers in the refrigerant manufacturing process	No – US EPA is assuming that most of the TCE is consumed in producing the refrigerant
Solvent degreaser	>90	Large commercial/ industrial settings (adults)	No – Such exposure scenarios are more likely to be monitored/controlled in the workplace and by OSHA
Solvent degreaser	>90	Small commercial shop employees and non-users (all adults)	Yes – high content, possible frequent use (*i.e.*, chronic exposures)
Solvent degreaser	>90	Consumer users (adults >16 years old), non-users (all ages)	Yes – high content, assumed low frequent use (*i.e.*, acute exposures)
Plastic clear protective coating spray (hobbyists; arts/crafts)	20-30		Yes – low content, but likely most frequent use of consumer products evaluated (*i.e.*, acute exposures)
Film cleaner (hobbyists)	>90		No – although high content, use of negatives/cameras with film is thought to be low and so frequency of use is assumed to be negligible; there is the potential for frequent use by small population (*i.e.*, film developers)
Toner aide (home office)	15-20		No – low content, assumed less frequent use
Mirror edge sealant (hobbyist/home maintenance)	20-30		No – low content, assumed less frequent use

Consumers are individuals using the products listed in Table 1-1 in and around their home. Non-users are individuals physically close to the use activity as it occurs and/or living in the

user's residence. The consumer/hobbyist users are assumed to be adults (16 years or older), and the non-users could be any age.

Chapter 2: Sources and Environmental Fate of TCE

In this chapter, information on the physical and chemical properties and environmental fate of TCE is presented. There also is a brief summary of the production volume and general information on the uses of TCE in the US. All of these factors are important to understanding the potential risks of TCE to workers in this assessment.

A. Physical and Chemical Properties of TCE

TCE is a colorless liquid with a pleasant, sweet odor resembling that of chloroform. It is considered a VOC because of its moderate boiling point, 87.2 °C, and high vapor pressure, 73.46 mm Hg at 25 °C. TCE is moderately water soluble (1.280 g/L at 25 °C), and has a log octanol:water partition coefficient (K_{ow}) of 2.42. The density of TCE, 1.46 g/cm^3 at 20 °C, is greater than that of water. Table 2-1 lists the chemical/physical properties of TCE.

Table 2-1. Physical-Chemical Properties of TCE[a].

Property	Value
CASRN	79-01-6
Molecular weight	131.39
Molecular formula	C_2HCl_3
Physical state	Colorless liquid
Odor	Sweet, pleasant, resembles chloroform
Density	1.46 g/cm^3 @ 20 °C[b]
Flash point	90 °C (closed cup)[b]
Auto flammability	410 °C[a]
Viscosity	0.53 mPa·s @ 25 °C[c]
Refractive index	1.4775[e]
Dielectric constant	3.4 ε_0 @ 16 °C[c]
Melting point	-84.7 °C (measured)
Boiling point	87.2 °C (measured)
Vapor pressure	73.46 mm Hg at 25 °C (measured)[d]
Dissociation constant (pK_a)	Not applicable
Henry's law constant	9.85×10^{-3} atm-m^3/mole (measured)
Water solubility	1,280 mg/L at 25 °C (measured)
Log K_{ow}	2.42 (measured)

[a]SRC (2012).
[b]EC (2000).
[c]Weast and Selby (1966).
[d]Daubert and Danner (1989).
[e]O'Neil *et al.* (2001).

B. ENVIRONMENTAL FATE

The environmental fate of a compound is important to understanding potential exposures to its impact on specific environmental media (*e.g.,* water, sediment, soil, and plants) and target organisms of concern. TCE is a volatile liquid with high vapor pressure, moderate water solubility, and high mobility in soil. Most reported environmental releases of TCE are to air with much fewer releases to landfills and very little released to water (see Chapter 3, Section A, *Environmental Release and Exposure* Summary). If released to air, degradation by sunlight and reactants in the atmosphere is slow. If released to water, sediment, or soil, the fate of TCE is influenced by volatilization from the water surface or from moist soil and by microbial biodegradation under some conditions. The biodegradation of TCE in the environment is dependent on a variety of factors and so a wide range of degradation rates are possible (*i.e.,* ranging from days to years). Finally, TCE is not expected to bioconcentrate in aquatic organisms.

Fate in Air

TCE does not absorb light greater than 290 nm very well; therefore, degradation of TCE by direct exposure to light, if it is released to the atmosphere, is not expected to be an important fate process (US EPA, 1979a). TCE is expected to undergo relatively slow atmospheric hydroxy radical oxidation with an estimated atmospheric half-life of about 13 days (using Version 4.10 of EpiSuite,US EPA 2012a). Phosgene, dichloroacetyl chloride (DCAC), chloroform, and formyl chloride can be formed from the reaction of TCE with hydroxyl radicals (Kao, 1994; Gay *et al.*, 1976; US EPA, 1980).

Fate in Water

Volatilization from water surfaces will be an important fate process based upon TCE's measured Henry's law constant. However, its density may cause it to sink in the water column, potentially increasing the aquatic residence time of TCE. Volatilization half-lives in an experimental field mesocosm consisting of seawater, planktonic, and microbial communities ranged from 10.7 to 28 days (Wakeham *et al.*, 1983). TCE achieved only 19 percent of its theoretical biochemical oxygen demand (BOD) over the course of a 28-day incubation period using the closed bottle (Organisation for Economic Co-operation and Development [OECD] 301D) test, and thus is not considered readily biodegradable. It achieved 2.4 percent of its theoretical BOD using an activated sludge inoculum in the modified Ministry of International Trade and Industry (MITI, OECD 301C) test over the course of a 14-day incubation period. It was not inherently biodegradable in a Zahn-Wellens (OECD 302B) test. These studies suggest that TCE will biodegrade slowly in surface waters. However, slow photooxidation in water has been reported (half-life of 10.7 months) (Dilling *et al.*, 1975). Based on these studies, biodegradation and hydrolysis in surface waters are not expected to be important environmental fate processes.

Fate in Soil, Sediment, and Groundwater

TCE is expected to have high mobility in soil based on measured soil organic carbon partition coefficients ranging from 72 to 148. Volatilization of TCE from moist soil surfaces is expected to be an important fate process given its relatively high Henry's law constant. TCE is expected to volatilize from dry soil surfaces based upon its high vapor pressure.

Both laboratory tests and field studies in the environment show wide variation in TCE biodegradation rates. In some cases, laboratory studies have shown rapid biodegradation. TCE has been shown to biodegrade under aerobic conditions by methanotrophic microbes in the presence of other substrates and under anaerobic conditions (in suitable reducing environments) in the presence of other organic matter. Without competent microorganisms that can degrade TCE and favorable environmental conditions, TCE can persist in the environment on the order of years.

Aerobic biodegradation of TCE by specialized communities of microorganisms has been reported (Wackett *et al.*, 1989). Biodegradation of TCE has also been shown to occur under conditions where additional substrates have been added to the medium (Mu and Scow, 1994; Kao and Prosser, 1999; Wilson and Wilson, 1985). Mixed microbial cultures of methane-utilizing bacteria have been shown to degrade TCE in two days under aerobic conditions (Fogel *et al.*, 1986). However, there are several factors that can limit the aerobic biodegradation of TCE, including TCE concentration, pH, and temperature. Toxicity of the degradation products (*e.g.*, dichloroethylene, vinyl chloride, chloromethane) to the degrading microorganisms may also reduce the rates of biodegradation of TCE in aerobic soils.

Biodegradation of TCE also occurs under anaerobic conditions. Under these conditions, as might be seen in flooded soils, sediment, or aquifer environments, TCE is biodegraded *via* reductive dechlorination; the extent and rate of degradation are dependent upon the strength of the reducing environment and other factors (McCarty, 1996). TCE half-lives in the field for aquifer studies range from 35 days to over six years. Major products of biodegradation of TCE in groundwater include dichloroethylene, chloromethane, and vinyl chloride (HSDB, 2012).

TCE contamination exists in the subsurface environment as a result of spills and leaking transfer lines/storage tanks. Because of its density and low Koc, TCE will ultimately move downward in the soil until an impermeable barrier is reached. This may occur when a TCE spill is of sufficient magnitude or deep enough in soil for volatilization to be restricted. Once in soil, TCE can become associated with soil pore water, enter the gas phase because of its Henry's Law constant, or exist as a nonaqueous phase liquid (NAPL). It is possible that upward or downward movement of TCE can occur in each of these three phases, thereby increasing the areal extent of the original spill. Nonaqueous phase concentrations of TCE which are large enough to overcome capillary forces will move downward into the aquifer. Once the water table is penetrated, lateral flow may be mediated by the regional ground-water flow. Due to its high density, the movement of free-phase TCE is still directed vertically until lower permeability features are encountered. Once an impermeable layer is encountered, horizontal movement

will occur. Such movement may even be directed against the natural ground-water flow by the effects of gravity. Since permeability is a function of the liquid as well as the medium, the vertical movement of TCE through an aquifer is determined by geological properties of the aquifer material; *i.e.,* granular size of sand or clay lenses. TCE will tend to pool near these impermeable features. Water passing over and around these pools may solubilize TCE so that it can be spread throughout the aquifer. This pattern of release and distribution in aquifers and TCE persistence have led to the widespread detection of TCE in groundwater and drinking water supplies derived from the contaminated groundwater (US EPA, 1992).

Bioconcentration

TCE is not expected to bioconcentrate in fish, with measured bioconcentration factors (BCFs) in carp ranging from four to 17. TCE's low measured BCF value suggests that bioconcentration in aquatic organisms is low (NITE, 2012). The estimated upper trophic level bioaccumulation factor (BAF) for TCE is 24 (using Version 4.10 of EpiSuite,US EPA, 2012a).

Table 2-2 provides a summary of the environmental fate information for TCE.

Conclusions on Environmental Fate

TCE is a volatile liquid and if released to air, will be slowly degraded by atmospheric hydroxy radicals. If released to water, volatilization to the atmosphere will be an important fate process and biodegradation will be slow. In soil, TCE does not bind strongly to soil organic matter and if not biodegraded at an appreciable rate, TCE can migrate through soil to groundwater. Based on the experimental evidence and environmental fate data available, TCE is expected to have low bioaccumulation potential and moderate persistence.

Table 2-2. Environmental Fate Characteristics of TCE[a].

Property	Value
CASRN	79-01-6
Photodegradation half-life	13.2 days (estimated)
Hydrolysis half-life	Does not hydrolyze under environmental conditions[b]
Biodegradation	19% after 28 days (not readily biodegradable)[b]; 4% after 28 days (not inherently biodegradable)[b]; 100% after 2 days (anaerobic conditions using mixed march cultures)[b]; 2.4% after 14 days (not readily biodegradable)[c]
Bioconcentration	BCF = 4.3-17 (measured in carp at 0.070 mg/L)[c]; BCF = 4-16 (measured in carp at 0.007 mg/L)[c]; BCF = 17 (measured in freshwater fish at 0.0087 mg/L)[c]; BAF = 23.7 (estimated)[a]
Log K_{oc}	2.17 (measured in silty clay Nebraska loam)[c]; 1.94 (measured in silty clay Nevada loam)[c]; 1.86 (measured in a forest soil)[c]; 1.8 (estimated)
Fugacity (Level III Model)[b]	
Air (%)	35.4
Water (%)	54.2
Soil (%)	10.1
Sediment (%)	0.3
Persistence[d]	P2 (moderate)
Bioaccumulation[d]	B1 (low)

[a]US EPA (2012a).
[b]EC (2000).
[c]NITE (2012).
[c]US EPA (1999).

C. PRODUCTION VOLUME AND GENERAL INFORMATION ON USES

In 2011, global consumption of TCE was 945 million lbs with expected growth at about 1.5 percent annually over the next five years. The corresponding US consumption was 255 million lbs (Glauser and Funda, 2012). There were two US producers for TCE as of 2011: The Dow Chemical Company in Freeport, TX and PPG Industries, Inc. in Lake Charles, LA (Glauser and Funda, 2012)[2].

TCE production volumes of 100 to 500 million lbs were reported to EPA in 2006 under the Inventory Update Rule (IUR). In 2005, there were four known importers of TCE (Chemcentral Corporation; Ineos Chlor Americas, Inc.; JSL Chemical Corporation; and TR International, Inc.) reported in the IUR (US EPA, 2006b). Exports of TCE from the US have increased along with similar increases for all chlorinated solvents (80 percent in 2011, 72 percent in 2010) (ICIS, 2010, 2012). More information can be found in Appendix B.

TCE has historically had a wide range of uses drawn from various markets, including intermediate chemicals (for refrigerant and polyvinyl chloride [PVC] manufacture), industrial and commercial solvents, pharmaceuticals, insecticides, fumigant, textiles (processing and flame retardants), adhesives, and paints (as diluent) (Ash and Ash, 2009). However, as of 2011, most US consumption is attributable to two specific uses: 83.6 percent of total TCE production volume is used as an intermediate for manufacturing the refrigerant, HFC-134a (a major alternative to CFC-12), and 14.7 percent is used as a solvent for metals degreasing, with 1.7 percent attributed to "other uses" (Glauser and Funda, 2012)[3].

[2] This material includes data or information derived from IHS Products provided to the US EPA. IHS products have been provided to the US EPA for its internal use and in the context of a license agreement. By receiving and accessing this material, you agree that IHS is not liable to you or any third party for your use of and/or reliance on the IHS data and information contained in this document, and any such use shall be at your own risk.

[3] Ibid.

Chapter 3: Human Health Risk Assessment

This chapter has five major sections: (1) Environmental Releases and Exposure Summary; (2) Hazard Summary; (3) Risk Characterization; (4) Discussion of Uncertainties and Data Gaps; and (5) Conclusions.

A. Environmental Releases and Exposure Summary

TCE has been detected in air, water, and humans (US EPA, 2011c). In identifying exposure pathways for TCE, its volatility plays a major role, and the inhalation route of exposure is of primary importance and concern. This section characterizes the environmental releases of, and workplace and consumer/hobbyist exposures to, TCE.

ENVIRONMENTAL RELEASES OF TCE

General

There is potential for release of TCE to air, water, sediment, and soil from manufacture, processing, and use. As noted previously, the largest percentage of TCE production and importation is used as an intermediate in the manufacture of refrigerants (~84 percent). Because most of the TCE associated with this use is expected to be reacted to form another chemical, potential releases to the environment from the refrigerant use is unlikely to contribute to the TCE found in ambient air/water/human biomonitoring as described below. It is expected that a small percentage of TCE may be released as fugitive air emissions (*i.e.*, material lost during use). This consistent with the Toxics Release Inventory (TRI) data which indicates some of the highest fugitive and point source air releases reported for TCE come from the degreaser use (*i.e.,* roughly 15 percent of the production/importation volume in the US). Thus, while there is some potential for fugitive emissions, fugitive TCE releases from manufacture of refrigerants will not be considered in this risk assessment.

The US EPA developed a summary of ambient air monitoring (*i.e.,* measured) data for TCE in the US from 1999 to 2006 (as reported in US EPA, 2011c) that is provided in Table 3-1. These data suggest that TCE levels have remained fairly constant in the US since 1999, with an approximate mean value of 0.3 µg/m^3 (*i.e.,* which is equivalent to 5.6 x 10^{-5} ppm).

Table 3-1. TCE Ambient Air Monitoring Data (µg/m^3)[a].

Year	Number of Monitors	Number of States	Mean	Standard Deviation	Median	Range
1999	162	20	0.30	0.53	0.16	0.01-4.38
2000	187	28	0.34	0.75	0.16	0.01-7.39
2001	204	31	0.25	0.92	0.13	0.01-12.90
2002	259	41	0.37	1.26	0.13	0.01-18.44
2003	248	41	0.35	0.64	0.16	0.02-6.92
2004	256	37	0.32	0.75	0.13	0.00-5.78
2005	313	38	0.43	1.05	0.14	0.00-6.64
2006	258	37	0.23	0.55	0.13	0.03-7.73

[a] The US EPA's Air Quality System database at the AirData Web site: http://www.epa.gov/airdata/ (as summarized in US EPA, 2011c). Note that the data are not from a statistically based survey and cannot be assumed to provide nationally representative values.

Other releases of TCE may occur, such as TCE entering publicly owned treatment works (POTWs), which will likely result in releases to surface waters and air. Disposal of TCE wastes to Resource Conservation and Recovery Act (RCRA) Subtitle C landfills also occurs and is of potential concern because TCE has moderate persistence under certain environmental conditions, and it is volatile, water soluble, mobile in soil and groundwater, and present in landfills. Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and the Superfund Amendments and Reauthorization Act (SARA), the US EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) have established a prioritized list of substances most commonly found at facilities on the National Priority List (NPL) (ATSDR, 2011). The listing is based on the frequency of occurrence, toxicity, and potential for human exposure. TCE was ranked 16th out of 847 candidate substances for the 2011 ranking; only the top 275 are considered to be on the list.

Releases of TCE from Consumer Uses

TCE can be released to indoor air from the use of consumer products that contain it, as well as from vapor intrusion and volatilization from contaminated water supplies (US EPA, 2011c). Where indoor air sources are present, it is likely that indoor levels will be higher than outdoor levels (US EPA, 2011c). US EPA (2011c) discussed several studies that measured indoor levels of TCE, but did not include any monitoring data for use of consumer products containing TCE. Recent literature sources report a few TCE air and personal monitoring studies that were not included in US EPA (2011c); however, no monitoring data for use of consumer products containing TCE were found. Specifically, the literature search did not find any studies that measured emissions of TCE from the six consumer products identified for consideration in this risk assessment (see below).

Releases of TCE from Small Commercial Degreasing Operations

Halogenated solvent cleaning (degreasing) is widely used to remove grease, oils, waxes, carbon deposits, fluxes, and tars from metal, glass, or plastic surfaces (US EPA, 2006a, 2007b). The degreasing process is used in many industries, both large and small. An analysis of the North American Industry Classification System (NAICS) identified 78 different industries (NAICS codes are listed in Appendix C; data not shown, but available in US EPA (2008b).

There are two general types of degreasing machines: batch and in-line. Batch cleaning machines are the most common type, while in-line cleaners are typically used in large-scale industrial operations (US EPA, 2006a). The size of a degreasing machine is defined by the area of its solvent-to-air interface. Emissions from degreasing machines typically result from: (1) evaporation of the solvent from the solvent-to-air interface; (2) "carry out" of excess solvent on cleaned parts; and (3) evaporative losses of the solvent during filling and draining of the degreasing machine (US EPA, 2006a).

Use of TCE as a degreaser in an occupational/commercial setting will result in its releases primarily to air due to its volatility. The US EPA has developed an analysis of available information from the 2008 National Emissions Inventory (NEI), the 2010 TRI, and the NAICS to estimate TCE releases and occupational exposures from this use. These release estimates were used to estimate TCE exposures to workers in small commercial degreaser operations. Though these releases also could result in TCE exposure to the general population, such an analysis is outside the scope of this risk assessment.

The NEI is a comprehensive and detailed estimate of air emissions of both criteria and hazardous air pollutants (HAPs) from all air emissions sources; the NEI is prepared every three years by the US EPA (2008b)[4]. As background, point sources are stationary sources (*i.e.*, sources that remain in one place); a large facility that houses an industrial process is an example of a point source (US EPA, 2004a). Nonpoint sources refer to smaller, more diffuse sources; a variety of sources are categorized as nonpoint sources, including small industrial/commercial operations (US EPA, 2004a).

Data from the most recent NEI (US EPA, 2008b) were considered. Based on the 78 NAICS codes (identified in Appendix C), and in conjunction with Source Classification Codes (SCC), the Pollutant Name, and Unit Type descriptions from the NEI, it is possible to identify the reported number of TCE emission points from 2008 (see Table 3-2); 66 percent of TCE emissions in 2008

[4] For those interested, here are the specific data sources/files used:
ftp://ftp.epa.gov/EmisInventory/2008v2/nei2008v2_national_county_level_sector.zip;
ftp://ftp.epa.gov/EmisInventory/2008v2/2008neiv2_facility.zip;
http://www.epa.gov/ttn/chief/net/neip/appendix_6.mdb
At the following website: http://www.epa.gov/ttn/chief/net/2008inventory.html, under "SCC Data Files", there is an option to download data by pressing the "Download" button. The following data sets are relevant: 1) Point and 2) Nonpoint.

were from nonpoint sources (NPS), while approximately 34 percent were from point sources PS). Thus, approximately two-thirds of the estimated emission points for TCE come from nonpoint sources.

Table 3-2. The Number of TCE-Emitting Emission Points and Corresponding Total Annual Air Emissions of TCE as reported in the 2008 NEI (US EPA, 2008b).

Type of Emission Point	Reported Number of Emission Points	Total Annual Air Emissions (Lbs/Yr)
Point source (PS)	186	1,480,000
Nonpoint source (NPS)	1,779	2,860,000

The US EPA's TRI is a database that contains detailed information on environmental releases and transfers of certain listed toxic chemicals from industrial facilities; the TRI is maintained by the US EPA and is updated annually (TRI, 2012a). Based on the NAICS codes, the 2008 TRI can be queried to identify stack and fugitive air emissions of TCE (see Table 3-3). Thus, the NEI and TRI data from the same year (2008) can be compared.

Table 3-3. Total Annual Air Emissions of TCE as Reported in the 2008 TRI (TRI, 2012b).

Type of Emission	Total Annual Air Emissions (Lbs/Yr)
Stack air emissions	1,320,000
Fugitive air emissions	1,230,000

In 2008, based on the NAICS codes listed in Appendix C, total NEI TCE air emissions were approximately 1.7 times greater than those reported in the 2008 TRI[5]. Whereas the NEI is the US EPA's primary emissions inventory for HAPs and criteria pollutants, the TRI is another inventory that may be considered. The TRI provides releases to other environmental media (*e.g.*, land and water) besides air; however, the TRI may exclude releases from small-scale operations, the intended focus of this risk assessment (US EPA, 2004a, 2011e). In light of this, release values from the 2010 TRI will be referenced, but the TCE air emissions will be estimated/adjusted based on the comparison between the 2008 NEI and TRI data (1.7 times the TRI reported value).

Point sources include large industrial facilities; they can also include small industrial/ commercial facilities, which have traditionally been classified as nonpoint sources (US EPA, 2008b). However, the choice of whether small industrial/commercial facilities are classified as point or nonpoint sources is determined by the appropriate State, Local, or Tribal air agency (US EPA, 2008b). Thus, EPA assumed that point sources are representative of large industrial facilities, while nonpoint sources are assumed to be representative of small/commercial facilities.

[5] Derived by adding the total 2008 NEI emissions (1,480,000 + 2,860,000 = 4,340,000) and dividing this by the total 2008 TRI emissions (1,320,000 + 1,230,000 = 2,550,000), which results in 4,340,000/2,550,000 = 1.7.

For point source emissions, based on the Emissions Inventory System (EIS) Identifier and EIS Unit Identifier from NEI, it is possible to identify the number of unique facilities (154) and degreasing units (machines; 180) reporting TCE emissions in 2008 (or about 1.2 degreasing units/facility). These 154 facilities would be considered large industrial facilities rather than small commercial operations.

Assuming each reported nonpoint source represents a unique facility, and by applying the estimate of 1.2 degreasing units per facility to nonpoint sources, the number of facilities corresponding to the nonpoint sources in Table 3-2 can be approximated to be 1,483 (*i.e.,* 1,779 divided by 1.2 degreasing unit per facility), making the total number of degreasing facilities 1,637 (*i.e.,* 154 unique, large Industrial facilities, plus the 1,483 small industrial/commercial facilities).

Based on the NAICS codes listed in Appendix C and information reported in the 2010 TRI, EPA identified relevant releases of TCE from solvent cleaning/degreasing operations (see Table 3-4).

Table 3-4. Relevant TCE Releases from Solvent Cleaning in 2010.

Release Type	Total Annual Release (lbs/Yr)	Percentage of Air-Emitting Facilities also Reporting this Type of Release (Percent)
Fugitive air emissions	780,000	100
Stack air emissions	750,000	100
Surface water releases	70	5.5
Release to RCRA Subtitle C landfill	1,711	1.1
Release to other landfill	8,308	2.2

Source: US EPA (2011e).

By examining the SCC from the NEI, the cleaning machine type could be identified (see Table 3-5). Large industrial facilities are not typically classified as nonpoint sources (US EPA, 2008b). Based on this, in-line degreasing units also are not classified as nonpoint sources. For this assessment, EPA classified nonpoint sources as either batch vapor or batch cold units. Table 3-5 shows a total of 129 (*i.e.,* 116 batch vapor plus 13 batch cold units) of this cleaning/degreasing machine type. Thus, EPA determined that approximately 90 percent (*i.e.,* 116 out of 129) of the 1,779 nonpoint sources would be expected to be batch vapor degreasing units, while 10 percent would be expected to be batch cold degreasing units. General degreasing units were ignored in this calculation because they cannot be categorized; their type is unknown.

Table 3-5. Breakdown of Degreasing Cleaning Machine Type for Point Source TCE Emissions

Cleaning Machine Type	Number of Units	Percentage of Units	Total Annual Air Emissions (lbs/Yr)[a]
Open top vapor degreasing (batch vapor)	116	64	890,000
Conveyorized vapor degreasing (in-line)	11	6	120,000
Cold solvent cleaning (batch cold)	13	7	140,000
General degreasing units (unknown)	40	22	330,000

[a]The total is equal to 1,480,000 lbs as reported for point sources in Table 3-2.
Source: US EPA (2008c).

All the information described above and presented in Tables 3-2 through 3-5 was used to develop an estimate of TCE releases to air from small commercial degreasing operations (Table 3-6). An explanation of how these estimates were derived follows:

Air Releases

As indicated earlier, TCE air emissions from degreasing were estimated to be 1.7 times the 2010 TRI reported value. Also, based on the 2008 NEI, point sources (large industrial facilities) accounted for 34 percent of all air releases, while nonpoint sources (small industrial/ commercial facilities) accounted for a higher number, 66 percent. Thus, for small industrial/ commercial facilities, the "Annual Release" was calculated as follows: 1.7 × 0.66 × "Total 2010 TRI TCE Air Releases"; or 780,000 + 750,000 = 1,530,000. Thus, the final estimate for small commercial degreasing facilities emissions to air is:

$$1.7 \times 0.66 \times 1{,}530{,}000 = 1{,}720{,}000 \text{ lbs}$$

All Other Releases

The percentage values from Table 3-4 were applied to the number of facilities (1,483 small industrial/commercial facilities) to develop estimates for TCE release to other environmental media as presented in Table 3-6[6].

[6] Thus, as an example, the value for "Release per Facility" in Table 3-6 for releases to surface water was calculated as follows: "Annual release" (3,426 lbs) divided by the product of "Number of Facilities" (1,483 small commercial degreaser operations) x "Percentage of Air-Emitting Facilities Expected to also have this Type of Release" (0.055) = 3,426/82 = 42 lbs released to surface water per facility.

Table 3-6. Estimate of 2010 TCE Releases for Small Industrial/Commercial Facilities (n = 1,483).

Media of Release	Annual Release (Lbs/Yr)	Release per Facility (Lbs/Yr)	Percentage of Air-Emitting Facilities Expected to also have this Type of Release (Percent)
Air	1,720,000	1,160	100
Surface water	3,426	42	5.5
RCRA Subtitle C landfill	150,000	8,308	1.2
Other landfill	55,823	1,711	2.2
POTWs	245	5	3.3

To estimate worker exposure in small degreaser operations using environmental release data required some additional assumptions about working operations in small commercial degreasing operation. For the purposes of this assessment, small industrial / commercial degreasing processes are expected to operate 260 days per year for 2 hours per day (US EPA, 2001a). Thus, combining the information from environmental releases and assumptions for operations, the potential operating emission factors (amount of TCE released) were calculated as follows:

> "Annual Air Release per Facility" × "1 / Number of operating days per year" × "1 / Operating hours per day" × "1 hour / 60 minutes", OR (providing all units and conversion values)
>
> 1,160 lbs/yr × 454 grams/lb. × 1/260 days × 1 / 2 hours × 1 hour/60 minutes = 16.8 grams of TCE/minute

Depending on workplace controls (*e.g.*, local exhaust ventilation), average TCE emissions escaping into the workplace from Open Top degreasers (*i.e.,* the kind noted above in Table 3-5 as representative of nonpoint, or small commercial operations) can range from 2.57 to 27.29 grams of TCE per minute (Wadden *et al.*, 1989). For this assessment, EPA assumed that TCE emissions occur only during the hours of operation, and that the calculated and reported potential operating emission factors are of the same order of magnitude (see Table 3-7).

Table 3-7. Potential Operating TCE Emission Factors from Degreasing (Calculated and Reported Values).

Type of Facility	Calculated Potential Operating TCE Emissions Escaping into the Workplace (g TCE/Minute)	Reported Potential Operating TCE Emissions Escaping into the Workplace (g TCE/Minute)
Large industrial	27.47[1]	27.29 (Wadden *et al.*, 1989) 24.9 (US EPA, 2001a)
Small industrial/commercial	16.73	27.29 (Wadden *et al.*, 1989) 9.72 (US EPA, 2001a)

[1] Data/calculation not shown; information provided because it represents an 8-hour work shift and so is most comparable to the Wadden et al. data.

Calculating Exposures used in this Risk Assessment

This section characterizes exposures for the two scenarios that are the focus of this assessment: small industrial/commercial facilities, where TCE is used as a cleaning solvent (degreaser), and the hobbyist at home who may use TCE either as a degreaser or in an arts and crafts use scenario. For these scenarios, EPA also provided estimates for individuals who may be in the same building as the user, but are not physically near the user or use of the TCE product. These individuals are called bystanders or non-users.

Calculating Occupational/Worker Exposures to TCE from Degreasing

The National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1981 to 1983, estimated that 401,000 workers employed at 23,225 plant sites were potentially exposed to TCE in the US; about 17 workers were estimated per facility (ATSDR, 1997). This estimate is understood to include both workers who are and are not (occupational non-users) directly involved with solvent cleaning operations. EPA estimated the average number of workers directly involved with solvent cleaning operations as five workers per facility (US EPA, 2001a).

Appendix D presents the rationale and calculations for estimating inhalation exposures for workers and bystanders in small commercial/industrial degreasing facilities. Exposure estimates were calculated for bystanders (*i.e.,* those non-users, likely all adults, who may be in the building/room, but not physically close to the degreasing operation). Typical and worst-case values represent the range of room ventilation volumes (*i.e.,* 3,000 cubic feet per minute (min^{-1}) and 500 cubic feet per min^{-1}, respectively). Finally, the use of local exhaust ventilation (LEV) is important because it offers some control of TCE emissions and exposures. Results are shown in Table 3-8. These values were used to determine the range of exposures for the small commercial degreaser scenario in the risk assessment.

Table 3-8. Summary of Potential Workplace TCE Inhalation Exposures: Small Commercial Degreaser.

		Typical		Worst-Case		Number of Workers
		With LEV[4]	No LEV	With LEV	No LEV	
Worker[1]	Inhalation exposure (8-hour TWA[3], ppm)	2	17	6	63	7,415
Occupational bystander/non-user[2]	Inhalation exposure (8-hour TWA, ppm)	1	9	5	55	17,796

[1] Workers are directly involved with degreasing operations.
[2] Occupational Bystanders have the potential to be exposed to TCE but they are not directly involved with degreasing operations
[3] TWA = Time Weighted Average
[4] LEV = local exhaust ventilation

Consumer Exposures – Degreaser and Arts/Crafts Uses of TCE

TCE has been used in many different formulations and in many commercial and consumer products over the years. In March 2012, 12 consumer products from three manufacturers were found in the National Institutes of Health's (NIH)' Household Products Database that contained TCE. Further research confirmed that six of these products contained TCE (Table 3-9)[7]. The other six products were absent from the former product manufacturer's website or were determined not to contain TCE. Three of the six non-TCE containing products were reformulated (*i.e.,* using tetrachloroethylene, hydrotreated light distillate, dipropylene glycol n-propyl ether, dipropylene glycol methyl ether acetate, aliphatic petroleum solvent, or acetone instead of TCE); the other three products were discontinued. There may be other consumer and hobbyist products that contain TCE that EPA did not identify[8].

The six products highlighted in bold in Table 3-9 are auto products and arts and crafts aerosol spray products that may be used at home by hobbyists, as well as in commercial settings. Use of these products by hobbyists indoors, at home, may lead to inhalation exposure to users and other residents of the home. Dermal exposure to users may also occur, although there is a low concern for this exposure due to TCE's high vapor pressure. Ingestion exposure from the use of these products appears to be unlikely given the way they are used (*i.e.*, sprayed onto artwork).

[7] See attached document entitled: "Supplemental Product Information for the TSCA Workplan Chemical Risk Assessment of TCE (External Review Draft)" for further details on the results of the Household Products Database retrieval and for the Material Safety Data Sheets and other information retrieved from company websites.
[8] Though the search was not exhaustive, there were several spot cleaners for fabrics marketed to consumers, but none contained TCE; lists of ingredients were not available for a few of the spot cleaners.

Table 3-9. TCE Products in Household Products Database Retrieval.

Product	Percent TCE (as of March 2012)[a]
Lectra Clean 02018 heavy duty electrical parts degreaser	None
Lectra Clean 02120 Lectra Clean II non-chlorinated heavy duty electrical parts degreaser	None
Sprayway C-60 063 solvent degreaser	**>90**
Sprayway C-60 064 solvent degreaser	**>90**
Sprayway 073 brake parts cleaner	None
Sprayway 201 clear protective coating spray	**20-30**
Sprayway 205 film cleaner	**>90**
Sprayway 208 toner aide	**15-20**
Sprayway 209 mirror edge sealant	**20-30**
Sprayway 669 gravel guard	Product not found on manufacturer product list
Sprayway 732 industrial cleanup dry cleaner	Product not found on manufacturer product list
TrakAuto Trouble Free Rust Buster	Company no longer in business

[a] Percent TCE according to Material Safety Data Sheets retrieved from company websites in March, 2012 (See attached document titled "Supplemental Product Information for the TSCA Workplan Chemical Risk Assessment of TCE (External Review Draft).pdf").

In the absence of available emissions and monitoring data for use of consumer products containing TCE, EPA used a screening level modeling approach to assess consumer exposure. Of the six products confirmed (Table 3-9) to contain TCE, two hobbyist products, a clear protective coating spray and an aerosol solvent degreaser, were selected for exposure modeling.

The Exposure and Fate Assessment Screening Tool Version 2 (E-FAST2) Consumer Exposure Module (CEM)[9] was selected for the consumer/hobbyist exposure modeling because it generates inhalation exposure estimates for aerosol spray products such as the two TCE-containing products identified above. E-FAST2/CEM requires fewer inputs than do higher tier (more complex) indoor air models. For example, higher tier indoor air models require inputs for measured emission values (generally based on chamber studies), which usually are not available for the consumer products that are the subject of this exposure assessment.

The E-FAST2/CEM modeling for TCE included a combination of upper percentile, mean, and assumed (hypothetical) input values in the calculation of potential exposures. The resulting exposure estimates are characterized as hypothetical exposures. As explained more fully in the

[9] For further information on the E-FAST/CEM defaults or underlying equations, see the E-FAST documentation manual (US EPA, 2007a).

Supplemental Information,[10,11] these hypothetical exposures are more likely to be high-end exposures than they are to be central tendency exposures; thus they represent conservative exposure values[12].

OPPT did not locate consumer product survey data for hobbyist use patterns for the two hobbyist products, including mass of product used per event, duration of event, and events per year, so these values are hypothetical. Specific information and assumptions are provided in the Supplemental Information (notes 10 and 11); however, the general assumptions were:

- For the consumer degreaser scenario: 1 hour/event, two events/month
- For the consumer clear protective coating spray scenario: 0.5 hour/event, one event per week

It was assumed that these exposures represent unique and separate acute exposure events for both users and non-users. This was based primarily on the information mentioned in the Hazard section below in which a high end estimate for the half-life in humans is 51 hours. This suggests that from week to week there would be some residual TCE (or metabolite[s]) left over from the previous week, but EPA did not assume that the residual would be substantial or build up.

Exposure factors for age groupings, inhalation rates, body weights, and life expectancy are derived from the 2011 Exposure Factors Handbook (EFH; US EPA, 2011d) and replace the E-FAST2 defaults derived from the 1997 EFH (US EPA, 1997). The E-FAST2/CEM exposure estimates are potential dose rates that do not include any assumptions about absorption through the lung. Selected modeling results appear in Table 3-10. Details on modeling results appear in the attached Supplemental Information (notes 10 and 11).

Table 3-10. Estimated TCE Potential Acute Dose Rates from Use of Two Hobbyist Products Indoors at Residences as Determined by E-FAST.

Age (Yrs)	Clear Protective Coating Spray User ADR_{pot} (mg/kg-bw/day)	Clear Protective Coating Spray Non-user ADR_{pot} (mg/kg-bw/day)	Solvent Degreaser User ADR_{pot} (mg/kg-bw/day)	Solvent Degreaser Non-user ADR_{pot} (mg/kg-bw/day)
<1	NA	0.5	NA	3
1-2	NA	0.4	NA	3
3-5	NA	0.4	NA	2
6-10	NA	0.3	NA	2
11-15	NA	0.2	NA	1

[10] See attached document titled "Supplemental Information on E-FAST2 CEM Outputs (Degreaser Use) TSCA Workplan Chemical Risk Assessment of TCE (External Review Draft).docx").

[11] See attached document titled "Supplemental Information on E-FAST2 CEM Outputs (Clear Protective Coating Spray) TSCA Workplan Chemical Risk Assessment of TCE (External Review Draft).docx"

[12] High-end exposures represent values above a mean or median and may include the high end of an exposure distribution. A central tendency value represents some measure of the center of a distribution, such as an average or mean or median.

16-20	0.5	0.2	3	1
21-78	0.4	0.1	3	0.8

ADR_{pot} = potential acute dose rate; NA = not applicable

These values were converted to concentrations in air in ppm following the methodology presented in Appendix E. Table 3-11 presents the hobbyist exposure values that will be used in the risk assessment.

Table 3-11. Estimated TCE Inhalation Calculated Concentration in Air (Over the Course of a Day[a]) from Use of Two Hobbyist Products Indoors at Residences.

Age (yrs)	Clear Protective Coating Spray User ADR_{pot} (ppm)	Clear Protective Coating Spray Non-user ADR_{pot} (ppm)	Solvent Degreaser User ADR_{pot} (ppm)	Solvent Degreaser Non-user ADR_{pot} (ppm)
<1	NA	0.1	NA	0.8
1-2	NA	0.1	NA	0.8
3-5	NA	0.1	NA	0.8
6-10	NA	0.1	NA	0.8
11-15	NA	0.1	NA	0.8
16-20	0.4	0.1	2	0.8
>21	0.4	0.1	2	0.8

[a] See Appendix E for method.

B. HAZARD SUMMARY

In this section, a brief summary of the hazard information on TCE is presented and is followed by a discussion of the hazard data that were used in this risk assessment.

EPA identified a number of published hazard and/or risk assessments on TCE that have been conducted by numerous governmental bodies, review panels and others. Table 3-12 shows some of the major documents reviewed and used in this assessment.

Table 3-12. Hazard/Risk Assessment Documents Consulted for this Report.

US Government Reports	US NRC Reports	International Reports
US EPA IRIS Toxicological Review and RfD/RfC summary for TCE (US EPA, 2011c)	Gulf War and health, Vol. 2: Insecticides and solvents (IOM, 2003)	EU Risk Assessment (EC, 2004)
OPPT/AEGL for TCE (US EPA, 2008a)	Human health risks of TCE: Key scientific issues (NAS, 2006)	Australia (NICNAS, 2000)
ATSDR Toxicological Profile for TCE (ATSDR, 1997)	Contaminated water supplies at Camp Lejeune: Assessing potential health effects (NAS, 2009)	OECD/SIDS (1996)

	Review of studies of possible toxic effects from past environmental contamination at Fort Detrick: A letter Report (NAS, 2010)	

AEGL = Acute Exposure Guideline Level; RfC = reference concentration; RfD = reference dose

Toxicokinetics (Absorption, Distribution, Metabolism, and Excretion)

Absorption

TCE is fat soluble (lipophilic) and easily crosses biological membranes. Though there are quantitative differences across species and routes, TCE is readily absorbed into the body following oral, dermal, or inhalation exposure. Because of its lipophilicity, TCE can cross the placenta and also passes into breast milk.

Absorption following inhalation of TCE is rapid and depends upon exposure concentration, duration of exposure, and lung ventilation rate. Mammalian lungs have the capacity to metabolize TCE, but uptake and distribution is based largely on the blood:air partition coefficient, which ranges between 8.1 and 11.7 in humans and between 13.3 and 25.8 in rodents (US EPA, 2011c)[13].

Although this assessment focuses on inhalation exposure only, it is worth noting that following oral ingestion, TCE is rapidly absorbed from the gastrointestinal tract into the systemic circulation (*i.e.,* blood). Absorbed TCE is first transported to the liver where it is metabolized for eventual elimination (*i.e.,* "first-pass effect"). Also, US EPA (2011c) summarized several volunteer studies in which both TCE liquid and vapors were shown to be absorbed in humans *via* the dermal route. Following exposures of between 20 and 30 minutes, absorption was rapid, with peak TCE levels in expired air occurring within 15 minutes (liquid) and 30 minutes (vapor).

Distribution

Regardless of the route of exposure, TCE is widely distributed throughout the body. The major determining factor in its distribution is the blood: tissue partition coefficient[14]. Other important factors include age-dependencies (*i.e.,* largely based on anatomical and physiological parameters such as metabolic and ventilation rates) and TCE binding to tissues/cellular components. Human data and data from animals indicate TCE levels can be found in many different tissues including: brain, muscle, heart, kidney, lung, liver, and adipose tissues. Human data also document levels of TCE in maternal and fetal blood and in the breast milk of lactating women. It is difficult to interpret the available human data given the lack of accurate information on source and extent of exposures.

US EPA (2011c) summarized many experiments in animals that quantify TCE levels in various tissues in rodents following oral and inhalation exposures, some of which provide key

[13] For ease in reading, "the IRIS program" will be used often to refer to this reference.

[14] This represents the ratio of the concentration of TCE in blood to the concentration of TCE in tissue. When the ratio is much less than 1, more TCE would be found in tissue rather than in the circulating blood.

data/parameters for the physiologically-based pharmacokinetic (PBPK) model used to derive the EPA's reference concentration (RfC) and reference dose (RfD)[15].

Metabolism

The metabolism of TCE has been extensively studied; the resulting metabolites play a key role in the toxicity of TCE. Of additional importance are the many TCE metabolites that also are known metabolites of other, similar compounds to which people may be exposed (see Table 3-13). This may be important in determining exposures because people may be co-exposed to many of these solvents at the same time (*e.g.*, DCA as disinfection by-products of chlorination of drinking water supplies) (Johnson *et al*., 1998).

Table 3-13. Common Metabolites of TCE and Related Compounds[a]

Parent → / Metabolites ↓	Tetrachloro-ethylene	1,1,2,2,-Tetrachloro-ethane	TCE	1,1,1-Trichloro-ethane	1,2,-Dichloro-ethylene	1,1-Dichloro-ethane
Oxalic acid		X	X		X	
Chloral	X		X			
Chloral hydrate	X		X			
Monochloroacetic acid	X	X	X	X	X	X
Dichloroacetic acid (DCA)	X	X	X			X
Trichloroacetic acid	X	X	X	X		
Trichloroethanol	X	X	X	X		
Trichloroethanol-glucuronide	X	X	X	X		

[a]Adapted from Table 2-1 in US EPA (2011c).

A comprehensive review of the metabolism of TCE in humans and rodents was provided in the IRIS document (US EPA 2011c). Animals and humans extensively metabolize TCE. The two major metabolic pathways are oxidative metabolism *via* the cytochrome P450 (CYP) mixed function oxidase system and glutathione (GSH) conjugation, the latter followed by further transformations with other enzymes. Both pathways are saturable, and above the saturable concentration/dose, TCE is excreted unchanged in expired air. According to US EPA (2011c), there was no metabolic saturation achieved in the human studies reviewed. However, in animal studies when metabolic saturation was achieved, 43 to 78 percent of TCE was exhaled as unchanged TCE in rats with a lower amount (from 10 to 18 percent) observed in mice.

[15] The RfC/RfD as defined by the IRIS program (http://www.epa.gov/iris/help_ques.htm#rfd): "RfD (expressed in units of mg of substance/kg body weight-day) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. An RfD can be derived from a no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. The inhalation RfC (expressed in units of mg of substance/m^3 air) is analogous to the oral RfD but provides a continuous inhalation exposure estimate."

Table 3-14 presents the important metabolites formed following both the CYP (oxidation) and GSH (conjugation) pathways. The amount and types of metabolites formed are important for understanding the toxicity of TCE in both animals and humans.

Table 3-14. TCE Metabolites Identified by Pathway[a].

Oxidative Metabolites[b]	GSH Conjugation Metabolites[c]
Chloral; metabolized to TCOH	DCVG; metabolized to DCVC isomers (there are different theories as to how the presumed toxic metabolite intermediate [DCVT] is formed; see text)
TCE oxide; re-arranged to DCAC	
TCOH; metabolized to TCOG	
TCA; may lead to DCA	

[a]In humans and animals.
[b]*In vitro* data suggest that rodents have a greater capacity to metabolize TCE *via* this pathway.
[c]There are sex and species differences in this metabolic pathway (see text).
DCVC = either S-(1,2-dichlorovinyl cysteine) [1,2-DCVC] or S-(2,2-dichlorovinyl cysteine) [2,2-DCVC];
DCVG = S-dichlorovinyl-glutathione; DCVT = dichlorovinyl thiol; TCOG = trichloroethanol, glucuronide conjugate;
TCOH = trichloroethanol

A review of *in vitro* data suggests that rodents (*i.e.,* especially mice) have greater capacity to metabolize TCE *via* the oxidation pathway (US EPA, 2011c). In addition, although there doesn't appear to be large sex- or age-dependent differences in TCE oxidative metabolism, there may be substantial differences in humans based on the existence of CYP isoforms and/or genetic polymorphisms.

Normally, conjugation is a process that leads to detoxification; however, this is not the case for many halogenated alkanes and alkenes, including TCE. For TCE, the eventual metabolite(s) of concern are formed several steps from the initial GSH conjugate formed in the liver, which ultimately results in toxicity or carcinogenicity in the kidney. The key GSH metabolite is one of two cysteine conjugate isomers; either S-(1,2-dichlorovinyl cysteine) [1,2-DCVC] or S-(2,2-dichlorovinyl cysteine) [2,2-DCVC], which can be further metabolized *via* N-acetylation to N-acetyl-S-(1,2-dichlrovinyl)-L-cysteine (or the 2,2-dichlorovinyl one)—NAcDCVC.

There are various theories about how DCVC is toxic to the kidney and, to a lesser extent, the liver. One theory states that a β-lyase enzyme catalyzes the breakdown of 1,2-DCVC to S-dichlorovinyl thiol (DCVT), an unstable intermediate that rearranges to other metabolites (enethiols) that form covalent bonds with cellular nucleophiles and results in toxicity. Another theory is that there is a kidney enzyme (L-alpha-hydroxy [L-amino] acid oxidase) that can form intermediates and keto acid analogues that decompose to DCVT. In rat kidney homogenates, this enzyme appeared to be responsible for up to 35 percent of the GSH pathway. However, this enzyme is not found in humans. A third theory suggests involvement of sulfoxidation of either the cysteine (DCVC) or mercapturic acid (NAcDCVC) conjugates by flavin-containing monooxygenase and CYP3A enzymes, respectively.

In contrast to the CYP oxidation pathway, there appear to be sex and species differences in TCE metabolism *via* the GSH pathway (US EPA, 2011c). Animal data show that rates of TCE GSH conjugation in male rats/mice are higher than females. According to some *in vitro* data, the rates of DCVG production in liver/kidney cytosol are highest in humans, followed by mice, and then rats. *In vitro* data also suggest that γ-glutamyl transpeptidase (*i.e.,* GGTP, an enzyme involved in DCVC production) activity in kidneys seems to be highest in rats, then humans, and then mice.

Thus, the key in evaluating the TCE metabolism data is to determine the relative roles of CYP and GSH pathways. It appears that, in rodents, the oxidation pathway is clearly more dominant than the GSH pathway. US EPA (2011c) suggests that the GSH pathway may play a larger role in humans than it does in rodents, but there is substantial uncertainty about this given the available data. In fact, Jollow *et al.* (2009), using essentially the same data, suggested that rodents have a higher capacity to conjugate TCE with GSH and are thus more susceptible to kidney toxicity/cancer compared with humans.

US EPA (2011c) concluded the following regarding the metabolism of TCE:

> "In summary, TCE oxidation is likely to be greater quantitatively than conjugation with GSH in mice, rats, and humans. Some evidence suggests that the flux through the GSH pathway, particularly in humans, may be greater by an order of magnitude or more than the <0.1% typically excreted of NAcDCVC in urine…However, these data are not consistent with studies in other laboratories using different analytical methods, which report 2-5 orders of magnitude lower estimates of GSH conjugation. Because the reasons for these differences have not been fully determined, substantial uncertainty remains in the degree of GSH conjugation, particularly in humans." (US EPA, 2011c, p. 3-51).

Excretion

As noted earlier, the major routes of excretion are urinary (*i.e.,* predominantly with oxidative metabolites such as TCA and TCOH, with minor GSH metabolites), followed by exhalation of unchanged TCE; elimination (*i.e.,* as metabolized TCE) *via* feces and *via* exhalation are minor pathways. Table 3-15 provides elimination half-life values in humans and rodents from different conditions for total trichloro compounds (TTC) following TCE exposures.

Half-lives are useful indicators for bioaccumulation potential. Assuming first-order kinetics, >90 percent is eliminated after four half-lives and about 99 percent after seven half-lives (Shen, 2008). Thus, assuming a half-life of about 51 hours (*e.g.,* the longest value listed in Table 3-15), TCE would be mostly cleared by approximately 200 hours (*i.e.,* about eight days) with nearly complete clearance by approximately 350 hours (*i.e.,* a little over two weeks).

Table 3-15: Half-Life Data For TCE in Rats and Humans[a].

Elimination Route	Rats		Humans	
	Exposure Conditions	Elimination Half-life	Exposure Conditions	Elimination Half-life
Exhaled air	–	–	Inhalation: 100 ppm/4 hours[b] 6-38 ppm/0.5-1 hour[c] 1 ppm/6 hours[d]	 0.04, 0.67, 5.6 hours 8-44 hours 14-23 hours
Urine	Inhalation: 50, 100, and 200 ppm/ 8 hours[4]	14.3-15.6 hours (females); 15.5-16.6 hours (males)	Assumed Inhalation: Measured various metabolites for three post-exposure days in four exposure groups (no concentrations provided)[e]	Males: TTC (50.7 hours) Females: TTC (26-48.8 hours)
	Oral (gavage) Dose not given[f]	"complete" within 1-2 days	Experimental exposures in groups of two to five adults (no concentrations provided)[g]	TTC (31-50 hours)
			Inhalation: Occupational setting, six males and six females; males exposed to 200 ppm, females exposed to 50 ppm (duration not reported)[h]	Males: TTC (26.1 hours) Females: TTC (50.7 hours)

[a]All data taken from information presented in pp. 3-53 to 3-56 in US EPA (2011c).
[b]Sato *et al.* (1977) .
[c]Opdam (1989).
[d]Chiu *et al.* (2007) .
[e]Ikeda and Imamura (1973) .
[f]Green and Prout (1985); Prout *et al.* (1985); Dekant *et al.* (1984) .
[g]Nomiyama and Nomiyama (1971); Ogata *et al.* (1971); Stewart *et al.* (1970); Bartonicek (1962) .
[h]Ikeda (1977) .

Summary of Toxicity Information on TCE

A very brief overview of the TCE hazard database is presented. Based primarily on the IRIS Toxicological Review (US EPA, 2011c), the multiple studies identified for evaluation as points of departure (PODs)[16] for candidate RfCs (*i.e.,* specifically p-cRfCs values derived using PBPK modeling instead of an applied dose/concentration) for non-cancer endpoints are specifically identified below as they are used in evaluating the hazard for this risk assessment. These include three studies for liver toxicity; four studies on immunotoxicity; five studies each for the

[16] POD represents the derived value from the animal or human study. It can be the actual dose or concentration at which an effect was observed or a benchmark dose (BMD) calculated for a pre-defined response rate for that effect.

kidney and the nervous system; seven studies for developmental toxicity; and nine studies for reproductive toxicity. Because there was some overlap (*i.e.*, one study may be used for several endpoints), the total of number of different studies is 29. PODs were identified for each of the studies and are based on the identified route of exposure/units. All values were converted to concentrations in air by the US EPA (2011c) and are presented in later sections of this report.

TOXICITY FOLLOWING ACUTE (SHORT-TERM) EXPOSURE

This summary is taken from the Interim Acute Exposure Guideline Level (AEGL) document (US EPA, 2008a). AEGLs represent threshold exposure limits to which the general public may be exposed under emergency conditions (*e.g.,* an evacuation) for a short time (*i.e.,* acute) period from 10 minutes to eight hours (*i.e.,* five values for each AEGL level are established at 10 minutes, 30 minutes, and one, four, and eight hours). The development of these values involved a rigorous scientific review of acute toxicity data, first by a Federal Advisory Committee and then by a National Academy of Sciences (NAS) panel (see US EPA, 2012b for more information).

In humans, TCE odors can be detected at concentrations of ≥50 ppm, although the Level of Distinct Odor Awareness determined by the AEGL program is 337 ppm. Information on the toxicity of TCE in humans comes from either volunteer studies or case reports in the medical/ occupational literature. As mentioned previously, in the early part of the 20th century, TCE was used as a medical anesthetic. According to the AEGL program, the concentrations applied for this particular use ranged from 5,000 to 15,000 ppm for anesthetic use and from 3,500 to 5,000 ppm for use as an analgesic.

Volunteer studies have shown that acute exposure to TCE results in central nervous system (CNS) effects and irritation in humans. The AEGL document summarizes 14 different human volunteer studies conducted between 1969 and 1982. Most of these studies had limitations (*i.e.*, no control group, reporting of effects were subjective). However, EPA used two of the studies as the basis for the AEGL values reported below. Researchers (Vernon and Ferguson, 1969; Ferguson and Vernon, 1970; as reported in US EPA, 2008a) exposed eight male volunteers to 0, 100, 300, or 1,000 ppm TCE for a two-hour period (*via* a breathing tube) in two separate studies. In both cases, subjects performed six different tests to assess visual-motor function. The 1,000 ppm concentration in this study was the highest concentration used in any of the 14 volunteer studies. There were clear effects at that concentration in both studies (*i.e., subjective* symptoms such as CNS-depression, dizziness, and lethargy as well as reductions in performance of visual perception, steadiness, and a pegboard test[17]). Some subjects had similar effects at the middle concentration (300 ppm), with no such effects observed at the 100 ppm concentration.

[17] A pegboard test evaluates the ability of the subject to place pegs into holes. It is an indicator of hand eye coordination and motor effects.

The AEGL process proposed the values shown in Table 3-16. These values are considered interim and not yet final. Only three of the five AEGL values are presented because these coincide with the time frames of interest for this risk assessment[18].

Table 3-16. Proposed AEGL Values for TCE (in ppm)[a].

Classification	30-Minute Value	1-Hour Value	8-Hour Value	Endpoint
AEGL-1 (non-disabling effects)	180	130	77	CNS (humans) Marginal CNS effects (not specified in original study, according to US EPA, 2008a), in 1/8 volunteers exposed to 300 ppm for 2 hours
AEGL-2 (disabling effects)	620	450	240	CNS (humans) Light-headedness, dizziness, or lethargy in combination with reduced performance in neurobehavioral test in volunteers exposed to 1000 ppm for 2 hours
AEGL-3 (lethal)	6,100	3,800	970	Mortality in mice (4600 ppm for 4 hours)

[a] Only the 30-minute, 1-hour, and 8-hour values are presented (representing the three time frames of interest in this assessment).

TOXICITY FOLLOWING REPEATED EXPOSURES (INCLUDING CANCER)

There are many studies in animals and humans that report effects in a variety of organ systems following exposure to TCE. The summary presented below is very brief and touches on the major points for each type of toxicity/cancer. For the purposes of this risk assessment, there was no attempt to re-review the majority of the original studies/literature, because a very thorough review was most recently published by the US EPA (2011c). A number of key studies were reviewed, and other assessment/reviews are referenced where appropriate.

Liver Toxicity (Including Cancer)

Animals and humans exposed to TCE consistently experience liver toxicity. Specific effects include the following structural changes: increased liver weight, increase in deoxyribonucleic acid (DNA) synthesis (transient), enlarged hepatocytes, enlarged nuclei, and peroxisome proliferation. In addition, US EPA concluded that TCE exposure causes liver tumors in mice but not rats and there is "…minimal support for association between TCE exposure and liver and gallbladder/biliary cancer" (US EPA, 2011c, p. 4-238).

[18] The clear protective coating spray use assumes a 30-minute exposure, the hobbyist degreaser use assumes one hour and the small commercial degreaser, although assuming only two hours of degreaser use, is reported as an eight-hour TWA.

Human Data

The US EPA (2011c) reviewed 21 non-cancer and 24 cancer studies in humans that evaluated effects on the liver. In the non-cancer studies, 13 were epidemiology studies evaluating the role of TCE exposure and liver cirrhosis. The US EPA concluded that the role of TCE exposure on liver cirrhosis could not be ruled out.

Five of the 21 human non-cancer reports were occupational studies, four of which were specifically TCE degreaser operations (Nagaya *et al.*, 1993; Rasmussen *et al.*, 1993; Xu *et al.*, 2009; Neghab *et al.*, 1997; as cited in US EPA, 2011c). Overall, the US EPA (2011c) concluded that "…these observations are suggestive of liver disorders as associated with potential TCE exposure, but whether TCE caused these conditions is not possible to determine given the study's limitations" (US EPA, 2011c, p. 4-221).

The human cancer studies evaluated included cohort, case-control, and community (geographic) studies that evaluated the following cancer types in humans: liver and biliary tract cancer, primary liver cancer, and gallbladder and extra-hepatic bile duct cancer (see Table 4-57 in US EPA, 2011c, for a summary of the 24 studies). Not all studies were used in the US EPA's meta-analysis, but the overall conclusions suggested a small, statistically significant summary relative risk (RRm) for liver and gallbladder/biliary cancer and TCE exposure.

Animal Data

The IRIS program devotes Appendix E, of its document, to evaluation of liver toxicity (primarily) to animals. The discussion revolves around two main issues: (1) understanding the events leading to liver tumors in rodents, and (2) determining the role of the various metabolites in that process (termed "co-exposure" by the IRIS program). In terms of the latter, many investigators have dosed animals with TCE, as well as with many of its metabolites to determine the role and potency of each in terms of target organ toxicity. It appears that the oxidation pathway is important for the development of liver toxicity, but the specific role of each metabolite (*i.e.*,that of TCA, DCA, and chloral hydrate), as well as the parent TCE, is unclear.

For non-cancer effects, many oral/inhalation studies in rats and mice were reviewed; US EPA (2011c) concluded that TCE exposure in animal studies does result in increased liver weight, a small, transient increase in DNA synthesis, enlarged hepatocytes, increased size of nuclei of liver cells, and proliferation of peroxisomes.

Liver effects (increase in liver/body weight ratio) observed in three animal studies (Kjellstrand *et al.*, 1983; Woolhiser *et al.*, 2006; Buben and O'Flaherty, 1985; as cited in US EPA, 2011c) were chosen by the IRIS program for use in the non-cancer dose-response assessment. NMRI mice were exposed to up to nine different TCE concentrations (ranging from 37 to 3,600 ppm) for various durations (1, 2, 4, 8, 16, or 24 hours/day) and for different time frames (from 30 to 120 days) (Kjellstrand *et al.*, 1983; as cited in US EPA, 2011c). The IRIS program calculated a benchmark dose, lower confidence limit (BMDL) of 21.6 ppm as a POD for an increase in the liver/body weight ratio from this experiment. In Woolhiser *et al.* (2006) (as cited in US EPA, 2011c), Sprague-Dawley rats were exposed to TCE *via* inhalation at concentrations of 0, 100,

300, or 1,000 ppm for six hours/day, five days/week for four weeks. As with the Kjellstrand *et al.* (1983) data, a BMDL of 25.2 ppm for increased liver/body weight ratio. Finally, the Buben and O'Flaherty (1985) data came from an oral study with Swiss-Cox mice (gavage, seven doses ranging from 100 to 3,200 mg/kg-bw/day plus control, five days/week for six weeks) and a BMDL of 81.5 mg/kg-bw/day was calculated as a POD for increased liver/body weight ratio.

In the cancer bioassays, $B6C3F_1$ mice (*via* inhalation and gavage routes) and Swiss mice (*via* inhalation) have consistently shown to have increased liver tumors following exposure to TCE. Gene marker studies cited by the IRIS program have shown specific mutation frequencies associated with tumors following exposure to TCE, TCA, DCA, and chloral hydrate. There is some overlap among the groups, but it is not clear what may be the predominant metabolite. Studies with rats do not report statistically significant increases in liver tumors.

Summary for Liver Toxicity/Cancer
For both cancer and non-cancer effects on the liver, the role of metabolites is important but not well understood. The oxidation pathway seems necessary for TCE-induced liver toxicity. Thus, IRIS concluded that multiple TCE metabolites (*i.e.,* and thus pathways) likely contribute to TCE-induced liver tumors.

Kidney Toxicity (Including Cancer)
Studies in both humans and animals have shown changes in the proximate tubules of the kidney following exposure to TCE. As with liver toxicity, TCE metabolites appear to be the causative agents that induce renal toxicity, including cancer. DCVC formation appears critical, because animals treated with DCVC alone show the same type of kidney damage as those treated with TCE.

Human Data
Eight human studies were reviewed by the IRIS program that evaluated kidney toxicity and over 35 epidemiological studies examining the possible relationship of kidney cancer and TCE exposure in humans.

All eight non-cancer studies evaluated workers (*i.e.,* for all degreasing operations) exposed to some level of TCE, and several followed renal cell carcinoma (RCC; or kidney cancer) or end stage renal disease cases. These studies showed increased levels of kidney damage (proximal tubules) exposed to "high" levels of TCE. Determining the level of TCE exposure was somewhat complicated and was expressed as one or more of the following descriptors: "intensity" × duration; job title; "ever exposed;" "high;" and "very high".

The more than 30 cancer studies with humans include evaluation of possible association of TCE exposure with cancer of the kidney and renal pelvis as well as RCC (the most common type of kidney cancer). US EPA (2011c) performed a meta-analysis of 15 cohort and case-control studies to evaluate the relationship between kidney cancer and TCE exposure, resulting in a summary relative risk (RRm) of 1.27 (95 percent confidence interval [CI] of 1.13 to 1.43). A

similar metric was determined for the 13 studies with higher TCE exposures (RRm of 1.64; 95 percent CI of 1.31 to 2.04).

There appears to be greater susceptibility to TCE exposure/kidney cancer in individuals with an active polymorphism in a gene associated with the GST metabolic pathway, which is associated with the β-lyase gene region (*i.e.,* which is responsible for converting DCVC to the presumed unstable intermediate DCVT). Also, there are some human studies suggesting a role for mutations to the tumor suppressor gene, von Hippel Lindau. US EPA (2011c) suggests that this tumor suppressor gene is inactivated in certain TCE-induced kidney cancers.

The US EPA concluded that TCE is "carcinogenic to humans" based on convincing evidence of a causal relationship between TCE exposure in humans and kidney cancer.

Animal Data

In the animal studies, renal toxicity was evident in both rats and mice following either inhalation or gavage exposures. The toxicity includes damage to the renal tubules (*e.g.,* both cytomegaly and karyomegaly). Under chronic gavage exposure scenarios, rodents exhibit almost 100 percent kidney toxicity induction. Under inhalation exposure scenarios, male rats are more susceptible than female rats or mice to kidney toxicity. As noted earlier, this toxicity is likely caused by DCVC formation, with possible roles for TCOH and TCA. Kidney effects observed in five animal studies were chosen by the IRIS program for use in the non-cancer dose-response assessment: three studies for histological changes in the kidney (Maltoni and Cotti, 1986; (NCI, 1976; NTP, 1988; as cited in US EPA, 2011c) and two studies for increases in the kidney/body weight ratio (Kjellstrand *et al.*, 1983; Woolhiser *et al.*, 2006; as cited in US EPA, 2011c).

The three studies that reported histological changes in the kidney of exposed animals included one inhalation and two oral exposure studies. The Maltoni and Cotti (1986) study (as cited in US EPA, 2011c) exposed Sprague-Dawley rats to TCE *via* inhalation (0, 100, 300, or 600 ppm) seven hours/day, five days/week for 104 weeks (and allowed all rats to continue unexposed until they died). A BMDL of 40.2 ppm was derived for renal tubular pathological changes (meganucleocytosis). The National Cancer Institute (NCI, 1976; as cited in US EPA, 2011c) reported an oral (gavage) 90-week study with $B6C3F_1$ mice (*i.e.,* dosed five days/week for 78 weeks, the final 12 weeks with no exposure) at doses ranging from 0 to 2,339 mg/kg-bw/day; a lowest-observed-adverse-effect level (LOAEL) was identified as the POD for toxic nephrosis. The National Toxicology Program (NTP, 1988) study (as cited in US EPA, 2011c) reported toxic nephropathy in Marshall rats exposed to TCE *via* gavage at doses of 0, 500, or 1,000 mg/kg-bw/day, five days/week for 104 weeks. The derived POD for this study was a BMDL of 9.45 mg/kg-bw/day.

The two studies that reported increases in kidney/body weight ratio that were used to develop PODs/p-cRfCs were both inhalation studies and were also used for the observed effects in the liver (Kjellstrand *et al.*, 1983; Woolhiser *et al.*, 2006; as cited in US EPA, 2011c). The PODs

developed were BMDL values for 34.7 ppm (Kjellstrand *et al.*, 1983) and 15.7 ppm (Woolhiser *et al.*, 2006).

Cancer bioassays with TCE in animals (*i.e.,* both gavage and inhalation exposure routes) did not show increased kidney tumors in mice, hamsters, or female rats, but did show a slight increase in male rats. Kidney tumors in rats are relatively rare (US EPA, 2011c).

Summary of Kidney Toxicity/Cancer

From a mechanistic standpoint, it is suggested that DCVC (and to a lesser extent other metabolites) is responsible for kidney damage and kidney cancer following TCE exposure (US EPA, 2011c). There are data that demonstrate that DCVC is delivered to the kidney following TCE exposure. Also, the genotoxicity of DCVC (see genotoxicity section below) further suggests that a mutagenic mode of action is involved, although cytotoxicity followed by compensatory cellular proliferation cannot be ruled out. There are possible roles for both genetic polymorphism (GST pathway) and mutations to tumor suppressor genes in the development of kidney cancers in humans following exposure to TCE.

Neurotoxicity

Neurotoxicity has been demonstrated in animal studies under both acute and chronic exposure conditions, and has been observed in human studies under acute conditions (chamber studies), as well as under chronic, occupational exposure conditions. The effects observed include alterations in nerve function, cognitive effects, sensory effects, and changes in psychomotor function, mood, and sleep behaviors. As already noted, due to these effects on the nervous system, TCE was initially synthesized for use as an anesthetic in humans in the early part of the 20^{th} century.

Human Data

The available human studies that evaluated neurotoxicity fall into three general categories: (1) evaluation of residents exposed to TCE (and sometimes other solvents) near Superfund sites; (2) occupationally exposed individuals (generally degreasers and generally studies already discussed above under either liver or kidney toxicity); and (3) short-term controlled experiments/studies with volunteers. Many different endpoints have been evaluated, and a brief review is presented below.

Thirteen studies were reviewed by the IRIS program, which concluded there was evidence of changes in trigeminal nerve function/morphology in humans following exposure to TCE. One of these studies was used in the dose-response assessment for neurotoxicity (*i.e.,* increased latency in the jaw muscle reflex [masseter reflex]) (Ruijten *et al.*, 1991; as cited in US EPA, 2011c). In that study, human mail printing workers (31 exposed and 28 controls) were evaluated for possible health effects from TCE exposure, defined as “cumulative exposure” (concentration × time). Using historical monitoring data mean exposures were calculated as 704 ppm × number of years worked, where the mean number of years was 16. The POD derived from the dataset was a LOAEL of 14 ppm (US EPA, 2011c).

Four studies evaluated effects on auditory function in humans; all reported effects from TCE exposure. All five studies that evaluated effects of TCE exposure on vision reported effects, one of which was the basis for one of the AEGL values discussed above (Ferguson and Vernon, 1970; Vernon and Ferguson, 1969; as reported in US EPA, 2008a). Ten studies evaluated cognitive functions such as learning and memory; the US EPA concluded that these studies "…collectively suggest cognitive function impairment" (US EPA, 2011c, p. 4-110).

There were nine human studies that specifically evaluated developmental neurotoxicity and exposure to TCE; four looked at birth defects (CNS defects and neural tube defects) and the remainder evaluated postnatal effects (delayed newborn reflex, impaired learning and memory, aggressive behavior, speech and hearing impairments, encephalopathy, impaired executive function, impaired motor function, attention deficits, and autism spectrum disorder). US EPA concluded that "… (W)hile there are broad developmental neurotoxic effects that have been associated with the TCE exposure, there are many limitations in the studies" (US EPA, 2011c, p. 4-568).

Animal Data

Dozens of animal studies were reviewed in US EPA (2011c) that evaluated many endpoints under a variety of exposure conditions; however, only the following four studies were used in the dose-response assessment to evaluate neurotoxicity.

Isaacson *et al.* (1990) (as cited in US EPA, 2011c) dosed weanling Sprague-Dawley rats *via* the oral route (drinking water) in an experimental protocol for an eight-week period. Animals were given no TCE for eight weeks (control group), 47 mg/kg-bw/day TCE for four weeks and then no TCE for four weeks ("5.5 mg/kg-bw/day group"), or 47 mg/kg-bw/day TCE for four weeks, no TCE for two weeks, and then 24 mg/kg-bw/day TCE for two weeks ("8.5 mg/kg-bw/day group"). From this study, a LOAEL of 47 mg/kg-bw/day for demyelination in the hippocampus was identified as the POD.

Male Wistar rats were exposed to TCE *via* inhalation to concentrations of 0, 50, 100, or 300 ppm for eight hours/day, five days/week for six weeks (Arito *et al.*, 1994; as cited in US EPA, 2011c). Electroencephalogram (EEG) responses were used to measure the number of wakeful hours versus sleep hours. A significant decrease in wakefulness was identified as the neurological effect; a POD of 14 ppm (*i.e.,* LOAEL, adjusted for continuous exposure) was identified.

Gash *et al.* (2008) (as cited in US EPA, 2011c) evaluated the effects of TCE (*i.e.,* oral gavage experiments with F344 male rats at doses of 0 or 1,000 mg/kg-bw/day, five days/week for six weeks) on dopamine-containing neurons in the CNS. The POD of 710 mg/kg-bw/day represents a LOAEL (adjusted for time) for loss of dopamine containing neurons.

The final animal neurotoxicity study used in the dose-response assessment for this endpoint is Kjellstrand *et al.* (1987) (as cited in US EPA, 2011c). In this study, the effect of TCE on regeneration of the sciatic nerve after a crush lesion was evaluated in mice (NMRI strain, males

only) and rats (Sprague-Dawley, females only). Animals were pre-exposed to TCE (0 or 300 ppm in rats and 0, 150, or 300 ppm in mice, both *via* inhalation and for 24 hours/day) for 20 days, the lesion was induced, and exposure continued for an additional four days prior to evaluation. The POD for this effect was a LOAEL of 300 ppm (rats) and 150 ppm (mice).

Summary of Neurotoxicity

Like kidney and liver toxicity, neurotoxicity is a well-documented effect in both humans and animals following exposure to TCE. The following effects were concluded to be a result of exposure to TCE by US EPA (2011c): alterations in trigeminal nerve function (humans); auditory effects (humans and animals); alterations in nystagmus (humans and animals); changes in vision (humans and animals); changes in cognitive function (humans and animals); changes in psychomotor effects (humans and animals); mood disturbance (humans and animals); sleep disturbance (animals); and developmental neurotoxicity (primarily animals).

Immunotoxicity (Including Cancer)

Immune-related effects following TCE exposures have been observed in both animal and human studies. In general, these effects were associated with inducing enhanced immune responses as opposed to immunosuppressive effects. Of concern are the indirect effects of immune hypersensitivity (*i.e.*, development of cancer *via* faulty tumor surveillance by a compromised immune system, and atherosclerosis).

Two of the three key studies used to derive the US EPA's RfD, one of which was also used to derive the RfC, were immunotoxicity studies in mice (Keil *et al.*, 2009; Peden-Adams *et al.*, 2006); because the latter is a developmental study, it is discussed in the *Developmental Toxicity* section below). In all, four animal studies evaluating immunotoxicity were used in the non-cancer IRIS dose-response assessment. Also, one of the three cancers for which the US EPA (2011c) based its cancer findings was non-Hodgkin's lymphoma (NHL) (the other two being kidney and liver cancer).

Human Studies

US EPA (2011c) found only limited evidence of immunosuppression, asthma, and allergies in the three studies reviewed. However, Arif and Shah (2007) did not find an association between TCE[19] exposure (as measured with passive monitors in NHANES participants over a 48- to 72-hour period; geometric mean reported levels were 0.03 µg/m^3 [95 percent CI of 0.02 to 0.04]) and asthma in 550 individuals in that study.

There is evidence for high TCE exposures in the workplace leading to a generalized hypersensitivity skin disease. As summarized in US EPA (2011c), a number of studies published since 1995—largely from Asian countries reflecting recent industrialization in those areas—report a skin disorder (not contact dermatitis) that includes systemic effects (hepatitis, lymph

[19] In their paper, Arif and Shah (2007) use the abbreviation TCE for perchloroethylene and trichloroethylene is identified as trichloroethene. In this assessment, the acronym TCE means the trichloroethene results from the Arif and Shah (2007) paper.

nodes, and other organs). These were seen in workers exposed to high levels of TCE in air (from ~9 to >700 ppm). The US EPA (2011c) performed a meta-analysis of a number of human studies evaluating a possible connection between scleroderma *i.e.,* (an autoimmune disease) and TCE exposure. Results indicated a significant odds ratio (OR) in men with a lower (not significant) increase in women. These results may not reflect a true gender difference in response because the incidence of this disease is very low in men (approximately one per 100,000 per yr) and somewhat higher in women (approximately one per 10,000 per yr).

Finally, in a study of degreasers, there was an increase in human inflammatory cytokine levels following TCE exposure (Iavicoli *et al.*, 2005; as cited in US EPA, 2011c). These findings are supported by studies in auto-immune prone mice (described below) in which short exposures to TCE result in increased levels of inflammatory cytokines. What does this mean then?

Animal Data

The following is a short description and identification of the PODs for the four immunotoxicity studies identified for consideration in the dose-response analysis for immunotoxicity.

Keil *et al.* (2009) exposed two strains of mice ($NZBWF_1$ mice, genetically prone to develop autoimmune disease, and $B6C3F_1$ mice, a standard test strain not genetically prone to develop autoimmune disease) to TCE *via* drinking water for 27 or 30 weeks at concentrations in water of 0, 1.4, or 14 ppm. A variety of immune system markers were measured. TCE did not affect some markers (natural killer cell activity or T- and B-cell proliferation) in either strain. However, other findings showed an increase in renal pathology scores (low concentration only; not observed at the high concentration), a significant decrease in thymus weight concentrations (both concentrations), and increased anti-dsDNA (at several time points, at both concentrations) in the $B6C3F_1$ strain. Two PODs were identified in this study, both at the same level (LOAEL of 0.35 mg/kg-bw/day for two different effects: decreased thymus weight and an increase in anti-dsDNA).

In an inhalation study, Kaneko *et al.* (2000) (as cited in US EPA, 2011c) exposed auto-immune prone mice to TCE at concentrations of 0, 500, 1,000, or 2,000 ppm for four hours/day, six days/week, for eight weeks. There were changes in organs associated with immune response (liver inflammation, splenomegaly, and hyperplasia of lymphatic follicles); a LOAEL of 70 ppm was used as the POD for these effects.

There were two studies that evaluated immunosuppression in rodents. In Sanders *et al.* (1982) (as cited in US EPA, 2011c), male and female CD-1 mice were given TCE in drinking water concentrations of 0, 0.1, 1.0, 2.5, or 5.0 mg/mL for four or six months. Immunity was suppressed in females only; a POD of 18 mg/kg-bw/day was identified as a LOAEL for inhibition of cell-mediated immunity and bone marrow stem cell activity. Another study that has already been discussed for evaluating both liver and kidney effects (Woolhiser *et al.*, 2006; as cited in US EPA, 2011c) also reported immunosuppressive effects (decreased plaque-forming cell [PFC] assay response) in rats exposed to TCE *via* inhalation for four weeks. In that study, a BMDL of 24.9 ppm was identified as a POD for this immunosuppressive effect.

Summary of Immunotoxicity
US EPA (2011c) concludes that "…the human and animal studies of TCE and immune-related effects provide strong evidence for a role of TCE in autoimmune disease and in a specific type of generalized hypersensitivity syndrome, while there are less data pertaining to immunosuppressive effects" (US EPA, 2011c, p. 4-627).

Reproductive Toxicity
Available human and animal data suggest possible reproductive effects in males, but not in females following exposure to TCE. Nine reproductive studies were used by the IRIS program in their dose-response assessment for this endpoint, including one human study.

Human Studies
Twelve human studies were evaluated; and most looked at potential effects in both males and females. One of the 12 studies was carried forward in US EPA (2011c) for the dose-response assessment. In that study (Chia *et al.*, 1996; as cited in US EPA, 2011c), a cohort of 85 workers in an electronics factory was selected, and 12/85 were monitored to assess exposure. The mean TCE exposure (*via* inhalation) after an eight-hour shift of these 12 workers was 29.6 ppm (range of nine to 131 ppm). There were no controls in the study. Males experienced decreased normal sperm morphology and other sperm effects (hyperzoospermia); a BMDL of 1.4 ppm was identified as the POD for these effects.

Overall, US EPA concluded that the TCE studies in humans showed a decreased incidence of fecundability (time-to-pregnancy) and menstrual cycle disturbances in women and the following effects in males: altered sperm morphology, hyperzoospermia, altered endocrine function, decreased sexual drive and function, and altered fertility.

Animal Data
Seven inhalation (all with males only) and eleven oral (both males and females evaluated) studies were evaluated to assessed reproductive effects in animal studies. Eight of these studies were carried into the dose-response evaluation and are briefly described below. Overall, the data support findings seen in humans in that females appear to be less affected than males.

There were five inhalation animal studies that evaluated reproductive toxicity and were used in the IRIS dose-response assessment; all of these studies focused on effects on the male. Xu *et al.* (2004) (as cited in US EPA, 2011c) exposed male CD-1 mice to TCE at concentration of 0 or 1,000 ppm for six hours/day, five days/week for six weeks. Sperm from treated animals resulted in decreased *in vitro* sperm-oocyte binding and *in vivo* fertilization; a POD of 180 ppm (LOAEL) was identified for this effect. In two separate experiments (Kumar *et al.*, 2000; Kumar *et al.*, 2001; as cited in US EPA, 2011c), male Wistar rats were exposed to TCE *via* inhalation at concentrations of 0 or 376 ppm. Both study protocols reported exposures of four hours/day, five days/week, but in the 2000 report, exposures were from two to 10 weeks, followed by an unexposed time frame of between two and eight weeks. In the 2001 report, exposures were

for either 12 or 24 weeks. Effects on sperm and reproductive tract effects (decreased testes weight, smaller, necrotic spermatogenic tubules, and other effects) were observed and PODs for these two types of effects were derived; LOAELs of 45 ppm.

Importantly, there was an increase severity in the effects when exposure duration went from 12 to 24 weeks. The final two inhalation studies evaluated effects on the male reproductive tract of CD-1 male mice exposed to 0 or 1,000 ppm TCE for six hours/day, five days/week for either 19 days over a four-week period (Forkert *et al.*, 2002; as cited in US EPA, 2011c) or for one to four weeks (Kan *et al.*, 2007; as cited in US EPA, 2011c). Sloughing of epididymal epithelial cells were observed in treated mice, and increased in severity with duration of exposures. A LOAEL of 180 ppm was identified as a POD for this effect.

The three oral animal studies selected for dose-response assessment for reproductive toxicity evaluated effects on males (DuTeaux *et al.*, 2004; as cited in US EPA, 2011c), female reproductive outcomes (Narotsky *et al.*, 1995; as cited in US EPA, 2011c), and reproductive behavior in both genders (NTP, 1986; as cited in US EPA, 2011c).

DuTeaux *et al.* (2004) (as cited in US EPA, 2011c) treated two strains of male rats (Sprague-Dawley or Simonson albino) by TCE exposure *via* the drinking water (0, 0.2, or 0.4 percent, resulting in doses of 0, 143, or 270 mg/kg-bw/day for 14 days). Results showed decreased fertilization (as measured by *in vitro* fertilization of oocytes from untreated female rats) at both concentrations in both rats strains, with a LOAEL of 141 mg/kg-bw/day identified as a POD. Narotsky *et al.* (1995) (as cited in US EPA, 2011c) treated F344 rats *via* gavage during gestation (nine days) to TCE at doses of 0, 475, 633, 844, or 1,125 mg/kg-bw/day. The study was a prequel to a complicated protocol with other chemicals in a mixture study; however, delayed parturition was seen at all dose levels and was used as a POD (LOAEL = 475 mg/kg-bw/day). In an NTP (1986) study (as cited in US EPA, 2011c), F344 rats were exposed to TCE *via* the diet (TCE placed in microcapsules and incorporated into feed) at estimated internal doses of 0, 72, 186, or 389 mg/kg-bw/day. Male and female animals were treated for one week pre-mating, then for 13 weeks, and then pregnant females were continued on treated diet throughout gestation. Results showed a decrease in mating and the LOAEL of 389 mg/kg-bw/day was used as the POD for consideration in the dose-response assessment.

Summary of Reproductive Toxicity

Overall, the US EPA concluded: "…the human and laboratory animal data together support the conclusion that TCE exposure poses a potential hazard to the male reproductive system" (US EPA, 2011c, p. 4-629).

Developmental Toxicity

Because the US EPA RfC is based primarily on a developmental endpoint (*I.e.,* congenital cardiac defects or heart malformations), considerable attention has been given to this issue in the literature. US EPA (2011c) evaluated many different developmental outcomes in both human and animal studies, including prenatal (*i.e.,* death, decreased growth, and congenital malformations) and postnatal (*i.e.,* growth, survival, developmental neurotoxicity,

developmental immunotoxicity, and childhood cancers) effects. There are seven animal studies used to develop PODs for eight different endpoints; all briefly described below.

Human Studies

The US EPA evaluated numerous studies—both occupational and geographically-based—in humans to examine the possible association of TCE with various developmental outcomes. Most of these studies have been mentioned earlier and represent workplace exposures (Finnish studies of Taskinen *et al.*, 1989; Taskinen *et al.*, 1994; both as cited in US EPA, 2011c); the geographic studies in Arizona, CO (Rocky Mountain Arsenal) and Woburn, MA. Some have focused on reproductive/developmental outcomes (ATSDR studies in Endicott, NY and the Camp Lejeune studies, the latter of which was the subject of an NAS investigation) (NAS, 2009).

US EPA (2011c) concluded that there are positive associations between TCE exposures and the following developmental effects in humans: spontaneous abortions, miscarriage, pre- and/or post-implantation loss, perinatal death, reduction in live births, decreased birth weight, small for gestational age, postnatal growth, cardiac defects, eye/ear birth anomalies, oral cleft defects, kidney/urinary tract disorders, musculoskeletal birth anomalies, anemia/blood disorders, and lung/respiratory tract disorders.

Since the publication of the IRIS Toxicological Review in 2011, one recent update for the Endicott, NY community was published by the NY State Health Department that evaluated maternal exposure to TCE and other VOCs and pregnancy outcome (Forand *et al*., 2012). The study evaluated all births recorded in Endicott, NY from either 1978 to 2002 (to assess low birth weight, pre-term and fetal growth) or from 1983 to 2000 (birth defects). The comparison group was the rest of NY State except for the city of New York. A large chemical spill occurred in the town in 1979, and monitoring of the contaminant plume occurred for years. Residents obtain their drinking water from an uncontaminated water source; however, TCE and other VOCs have been measured in groundwater, soil, and inside buildings, the latter due largely to vapor intrusion. The study authors reported significant adjusted rate ratios (RRs) for the TCE-contaminated area for, among others, the following endpoints: low birth weight (RR of 1.36; 95 percent CI of 1.07 to 1.73), small for gestational age (RR of 1.23; 95 percent CI of 1.03 to 1.48), and cardiac defects (RR of 2.15; 95 percent CI of 1.27 to 3.62).

Animal Data

There were five inhalation and 17 oral developmental toxicity studies with TCE in animals reviewed in US EPA (2011c); however, only five were considered in the dose-response assessment and only one was an inhalation study (Healy *et al.*, 1982; as cited in US EPA, 2011c) and the other four were oral studies.

Two developmental studies reported mortality (pre- and postnatal mortalities as resorptions). Healy *et al.* (1982) (as cited in US EPA, 2011c) exposed female Wistar rats to TCE *via* inhalation at concentrations of 0 or 100 ppm for four hours/day, for 13 days (gestation days eight to 21). There was an increase in resorptions at the only concentration tested and a LOAEL of 17 ppm was identified as a POD. The other study in which a POD was identified for mortality in the

developing fetus was the Narotsky *et al.* (1995) study (as cited in US EPA, 2011c) mentioned above in the reproductive toxicity section (gavage study with rats treated during gestation); resulting in a BMDL of 32.2 mg/kg-bw/day for resorptions as a POD. The Healy *et al.* (1982) study (as cited in US EPA, 2011c) was also used to derive a POD for reduced fetal weight (as a LOAEL of 17 ppm).

Johnson *et al.* (2003) reported data from different experiments over a several-year period in which pregnant Sprague-Dawley rats were exposed (*via* drinking water) to TCE at four different concentrations (0, 0.0025 ppm, 0.250 ppm, 1.5 ppm, and 1,100 ppm) for the duration of their pregnancies (22 days). The authors concluded that there was a statistically and biologically significant increase in the formation of heart defects at the 0.250 ppm dose level at both the individual fetus level and the litter level. There was no statistical increase at the 1.5 ppm dose level (at either the individual fetus or litter level), but there was an increase at the highest concentration (1,100 ppm).[20] A BMDL of 0.0207 mg/kg-bw/day as a POD for heart malformations was identified (US EPA, 2011c).

There were two oral studies that evaluated developmental neurotoxicity and were used in the dose-response evaluation for developmental toxicity. Fredriksson *et al.* (1993) (as cited in US EPA, 2011c) treated male NMRI mouse pups with TCE *via* gavage (0, 50, or 290 mg/kg-bw/day) for six days (postnatal days [PNDs] 10 to 16) and then measured spontaneous activity in several ways on PNDs 17 and 60. Treated animals showed decreased rearing activity at both dose levels on PND 60 (but not PND 17), resulting in a LOAEL of 50 mg/kg-bw/day as a POD. In a rat study (Taylor *et al.*, 1985; as cited in US EPA, 2011c), pregnant female Sprague-Dawley rats were given TCE in their in their drinking water until 21 days post partum at concentrations of 0, 312, 625, or 1,250 mg/L. Male offspring from treated animals in the mid and high exposure groups showed increased exploratory behavior on PNDs 60 and 90, resulting in a derived LOAEL of 45 mg/kg-bw/day as a POD.

Finally, there was a developmental immunotoxicity study that was used as a critical study for developing the RfD (for oral exposure). Although not used for the RfC, it is described here because it is the only other critical study not otherwise mentioned. Peden-Adams *et al.* (2006) also exposed B6C3F1 mice to TCE *via* drinking water. Mice were exposed during mating and through gestation to TCE levels of 0, 1.4, or 14 ppm in drinking water. After delivery, pups were further exposed for either three or eight more weeks at the same concentration levels in drinking water. Suppressed PFC response was seen in male pups (after three and eight weeks of exposure) and female pups (only at eight weeks) at 1.4 ppm. Delayed hypersensitivity response was increased in the females exposed for eight weeks at this concentration. At the higher concentration (14 ppm), both of these effects were observed again, but were seen in both males and females at both time points (suppressed PFC response) or in both males and females only at eight weeks (increase in delayed hypersensitivity response). A LOAEL of 0.37

[20] The EPA Science Advisory Board (US EPA, 2011a) reviewed these data and suggested that the IRIS program use the Johnson *et al.* (2003) study as one of the critical/principal studies for RfD/RfC derivation.

mg/kg-bw/day served as a POD for the decreased PFC and increased delayed hypersensitivity responses (US EPA, 2011c).

Summary of Developmental Toxicity
The US EPA (2011c) concluded the following regarding developmental toxicity and TCE exposure:

> "Overall, based on weakly suggestive epidemiologic data and fairly consistent laboratory animal data, it can be concluded that TCE exposure poses a potential hazard for prenatal losses and decreased growth or birth weight of offspring… Epidemiological data provide some support for the possible relationship between maternal TCE exposure and birth defects in offspring, particularly cardiac defects" (US EPA, 2011c, p. 4-629).

Regarding studies of birth defects in animals, the US EPA concluded that there is potential for disruption of the development of the eye (from exposure to TCE and its oxidative metabolites) (US EPA, 2011c, p. 4-630), and although the cardiac defect studies have some limitations, their findings cannot be dismissed and are based on some mechanistic grounds (predominantly findings in developmental studies with chick embryo, and concordance in the stages of heart formation between mammals and birds) (US EPA, 2011c, p. 4-631).

Genetic Toxicity
TCE, and many of its metabolites, have been shown to be genotoxic. TCE, however, does not appear to be a direct-acting mutagen, but it does affect both DNA and chromosomes. In bacterial test systems, TCE does not induce mutations unless there is metabolic activation (*i.e.*, the presence of metabolizing enzymes). TCA, an oxidative metabolite of TCE, also does not induce mutations in bacterial test systems unless metabolic activation systems are present. However, other TCE metabolites (DCA, chloral hydrate, DCVG, and DCVC) all induce mutations without metabolic activation.

US EPA (2011c) evaluated data on TCE and the aforementioned metabolites in a variety of *in vitro* and *in vivo* test systems. Though it is thought that these metabolites may be responsible for TCE genotoxicity, US EPA (2011c) did not draw any conclusions on this matter, largely because there were not sufficient genotoxicity data with standard tests for all of the metabolites. However, the IRIS program did state that DCVC appears to have "predominantly resulted in positive data," supporting the conclusion that it is genotoxic (particularly in the kidney).

Hazard Summary
Table 3-17 provides a list of the 12 inhalation studies from which hazard values will be used in this risk assessment. There are at least two studies for each major target organ. Multiple species have been evaluated (*i.e.,* humans, mice, rats). Because some of the studies report more than one adverse outcome, 17 PODs (and therefore modeled human equivalent concentrations; explained more fully in the next section) were identified.

Table 3-17. Inhalation Studies Identified In US EPA (2011c) For Use In OPPT TCE Risk Assessment.

Target Organ	Species	Range of Doses or Concentrations[a]	Duration	POD Type[b]	Effect	HEC_{50} (ppm)	HEC_{99} (ppm)	Reference
Liver	Mouse	37-3,600 ppm	30-120 days	BMDL = 21.6 ppm	Increased liver weight/body weight ratio	25	9.1	1
	Rat	100-1,000 ppm	28 days	BMDL = 25 ppm		53	19	2
Kidney	Rat	100-600 ppm	104 weeks	BMDL = 40.2 ppm	Pathology changes in renal tubule	0.28	0.038	3
	Mouse	37-3,600 ppm	30-120 days	BMDL = 34.7 ppm	Increased kidney weight/body weight ratio	0.88	0.12	1
	Rat	100-1,000 ppm	28 days	BMDL = 15.7 ppm		0.099	0.013	2
Neuro-toxicity	Human	Mean exposure of CxT	Mean of 16 years	LOAEL = 14 ppm	Trigeminal nerve effects	14	5.3	4
	Rat	50-300 ppm	6 weeks	LOAEL = 12 ppm	Changes in wakefulness	13	4.8	5
	Rat	300 ppm	24 days	LOAEL = 300 ppm	Decreased regeneration of sciatic nerve	274	93	6
	Mouse	150-300 ppm	24 days	LOAEL = 150 ppm		378	120	
Immuno-toxicity	Mouse (auto-immune prone strain)	500-2,000 ppm	8 weeks	LOAEL = 70 ppm	Changes in immunoreactive organs	97	37	7
	Rat	100-1,000 ppm	28 days	BMDL = 24.9 ppm	Immunosuppression	29	11	2
Reproduct-ive toxicity	Human (male)	Mean exposure = 29.6 ppm	Measured values after an 8-hour work shift; mean years on job was 5.1	BMDL = 1.4 ppm	Sperm effects	1.4	0.5	8
	Mouse (male)	1,000 ppm	6 weeks	LOAEL = 180 ppm	Sperm effects	190	67	9
	Rat (male)	376 ppm	2-10 weeks, 12 weeks, 24 weeks	LOAEL = 45 ppm	Sperm effects and male reproductive tract effects	32	13	10

Table 3-17. Inhalation Studies Identified In US EPA (2011c) For Use In OPPT TCE Risk Assessment.

Target Organ	Species	Range of Doses or Concentrations[a]	Duration	POD Type[b]	Effect	HEC_{50} (ppm)	HEC_{99} (ppm)	Reference
	Mouse (male)	1,000 ppm	19 days over 4 weeks, 1-4 weeks	LOAEL = 180 ppm	Effects on epididymis epithelium	190	67	11
Develop-mental toxicity	Rat (female)	100 ppm	13 days (during gestation)	LOAEL =17 ppm	Increased resorptions	16	6.2	12
	Rat (female)	100 ppm	13 days (during gestation)	LOAEL = 17 ppm	Decreased fetal weight	16	6.2	12

[a]Controls (or zero dose/concentration) are not presented, so a sense of the lowest and highest values is understood.

[b]POD type can be NOAEL, LOAEL, or BMDL; the IRIS program adjusted all values to continuous exposure.

Reference List (all as cited in US EPA, 2011c):

1 = Kjellstrand *et al.* (1983)
2 = Woolhiser *et al.* (2006)
3 = Maltoni and Cotti (1986)
4 = Ruijten *et al.* (1991)
5 = Arito *et al.* (1994)
6 = Kjellstrand *et al.* (1987)
7 = Kaneko *et al.* (2000)
8 = Chia *et al.* (1996)
9 = Xu *et al.* (2004)
10 = Kumar *et al.* (2000); Kumar *et al.* (2001)
11 = Forkert *et al.* (2002); Kan *et al.* (2007)
12 = Healy *et al.* (1982)

Hazard Data to be used in Risk Assessment for TCE

The US EPA's IRIS program evaluates hazard and dose-response information on effects that may result from exposure to environmental contaminants. The results of their analyses are hazard values; an RfD or RfC to be used for non-cancer risk estimates and an oral slope factor or inhalation unit risk (IUR) factor for cancer risk estimates. In this risk assessment, the inhalation route of exposure was evaluated; therefore, cancer risks were assessed based on the IUR, and non-cancer risks were assessed based on the identified PODs from studies used to develop the US EPA's RfC.

Rather than use a single, point estimate value for the non-cancer risk assessment, a range of risk estimates are presented, thereby providing a range of data. This allows flexibility in evaluating or estimating risk based on exposure duration. Given the different exposure scenarios considered (both acute and chronic for small commercial degreasers, and just acute for the two consumer exposure scenarios), different endpoints were used based on the expected exposure durations. For non-cancer effects, both neurotoxicity and developmental toxicity could occur following acute (short-term) exposures, whereas other effects (toxicity to the liver, kidney, immune system, and the reproductive system) could occur following repeated exposure to TCE. Cancer risk estimates were only derived for chronic exposure scenarios. Other approaches, including use of the IRIS RfC, may be appropriate for other risk assessments.

The US EPA (2011c) non-cancer hazard PODs were derived using PBPK modeling. This model was reviewed by the SAB (US EPA, 2011a) and found to be both useful and sophisticated. The PODs for each endpoint to be used in this risk assessment are those for which a human equivalent concentration (HEC) was derived using this model developed by IRIS for TCE.

PBPK Modeling of TCE and its Metabolites

Given the complicated metabolic profile of TCE, understanding the relationship between the external dose/concentration (*i.e.*, exposure) and internal dose at the target organ of interest is critical to quantifying potential risk(s). US EPA (US EPA, 2011c) developed a detailed PBPK model for TCE and its metabolites designed to make such predictions of PODs. As part of building the model, the IRIS Toxicological Review provides a detailed summary of the history of TCE PBPK models that have been built over the years, resulting in an updated model reported in both Evans *et al.* (2009) and Chiu *et al.* (2009). This model was used to predict 14 different dose-metrics as measures of potential TCE toxicity (each dose-metric was developed to evaluate a different metabolic pathway/target organ effect based on the dose-response analysis and understanding of metabolism) (Table 3-18).

Table 3-18. U.S. EPA IRIS PBPK-Modeled Dose Metrics for TCE Dose-Response Assessment.

Dose-Metric Identifier	*Explanation of What the Dose-Metric Identifier Represents*
ABioactDCVCBW$^{3/4}$	Amount of DCVC bioactivated in the kidney per unit body weight[a]
ABioactDCVCKid	Amount of DCVC bioactivated in the kidney per unit kidney mass
AMetGSHBBW$^{3/4}$	Amount of TCE conjugated with GSH[b]
AMetLiv1BW$^{3/4}$	Amount of TCE oxidized in liver[c]
AMetLivOtherBW$^{3/4}$	Amount of TCE oxidized to metabolites other than TCA or TCOH (per unit body weight)
AMetLivOtherLiv	Amount of TCE oxidized to metabolites other than TCA or TCOH (per unit liver weight)
AMetLngBW$^{3/4}$	Amount of TCE oxidized in respiratory tract (per unit body weight)
AMetLngResp	Amount of TCE oxidized in respiratory tract (per unit respiratory tract tissue)
AUCCBld	Area under the curve of venous blood concentration of TCE[d]
AUCCTCOH	Area under the curve of blood concentration of TCOH
AUCLivTCA	Area under the curve of the liver concentration of TCA
TotMetabBW$^{3/4}$	Total amount of TCE metabolized (per unit body weight)[e]
TotOxMetabBW$^{3/4}$	Total amount of TCE oxidized (per unit body weight)[f]
TotTCAInBW	Total amount of TCA produced

[a] This was the dose-metric used to derive the IUR for kidney cancer and some non-cancer kidney effects.
[b] This was the dose-metric used for some non-cancer kidney effects.
[c] This was the dose-metric used to derive the IUR for liver cancer and the non-cancer liver effects.
[d] This was the dose-metric used to derive a reproductive toxicity endpoint (effects on male reproductive outcomes from one study; DuTeaux *et al.*, 2004; as cited in US EPA, 2011c).
[e] This was the dose-metric used to derive the cRfC for the immunological effect endpoint, some reproductive toxicity endpoints, some developmental toxicity endpoints, and neurotoxicity. It was also used to derive the IUR for NHL.
[f] This is the dose-metric used to derive the cRfC for the cardiac malformations (developmental) endpoint.

These dose-metrics were converted to daily or weekly average concentrations based on simulations lasting 10 weeks for rats/mice and 100 weeks for humans. The predicted values were compared across species, compared to *in vivo* data, and were also subjected to sensitivity analyses (all summarized in Section 3.5.6 in US EPA, 2011c).

The 32 different candidate PODs/HECs that were identified and developed by the IRIS program to inform the development of the RfC (primarily) were used to identify the range of hazard values that could be used in the current risk assessment. Appendix F contains a detailed table that presents all of the values. Table 3-19 provides a list of the values that will be used in this risk assessment by endpoint and exposure duration.

The data in Table 3-19 are from the 12 inhalation studies summarized in Appendix F. In this risk assessment, the lower-end of the range of hazard values for the "sensitive" human (the 99th percentile, or HEC_{99}) for each target organ/endpoint was used. These values are bolded in Table 3-19. To provide an indication of the variability in the HEC predictions, the range of

hazard values for the "typical" human (the 50th percentile or HEC_{50}) is also presented. In both instances, the terms "low-end" and "high-end" represent the minimum and maximum values within the data presented in Table 3-17 for the 12 inhalation studies used herein. Also, the third column in the table presents the original POD (*i.e.*, a benchmark dose value or LOAEL) prior to the use of the PBPK model to develop the HEC. Importantly, for five of the six target organs, the HEC value is reasonably close to the original POD (within a factor of ~2). The exception is the kidney, for which the HEC is between 100- and 1000-fold lower than the original POD.

Table 3-19. Range of TCE Candidate POD/HEC Values Derived by US EPA (2011c).

Exposure Duration	Target Organ	Original POD (Prior to PBPK Model)	Range (Minimum and Maximum) of HEC values (All Values in ppm)			
			By Target Organ (HEC_{50})[a]	By Target Organ (HEC_{99})[b]	By Exposure Duration (HEC_{50})	By Exposure Duration (HEC_{99})
Chronic	Liver	21.6[c] – 25[c]	25-53	**9.1**-19	0.28 – 190	0.013 - 67
	Kidney	40.2[c] – 34.7[c]	0.28 – 0.88	**0.013** – 0.12		
	Immune system	24.9[c] – 70[d]	29 - 97	**11**-37		
	Reproductive system	1.4[c] – 180[d]	1.4-190	**0.5**-67		
Acute	Nervous system	12[d] – 150[d]	13-378	**4.8**-120	**16-378**	4.8-120
	Developing organism	17[d]	16	**6.2**		

[a] HEC_{50} is the 50th percentile for the continuous concentration that leads to an internal dose in a human equivalent to the rodent internal dose POD.
[b] HEC_{99} is the lower 99th percentile for the continuous concentration that leads to an internal dose in humans equivalent to the rodent internal dose POD.
[c] BMDL, in ppm.
[d] LOAEL, in ppm.
Bolded values will be used in the risk assessment

C. HUMAN HEALTH RISK CHARACTERIZATION

Risk Estimation Approach for Acute and Repeated Exposures

For the current risk assessment (*i.e.,* targeted at the use of TCE as a degreaser in a small commercial shop and by a consumer and the spray fixative use by a hobbyist), a range of PODs identified in the US EPA (2011c) for TCE were used for non-cancer endpoints (Table 3-19). The IRIS IUR value for cancer also developed by US EPA (2011c) was used for cancer risk estimates for the chronic exposure scenarios.

The exposure scenarios evaluated in this risk assessment are shown in Table 3-20. For the worker scenario, non-cancer (acute and chronic) and cancer effects was evaluated. EPA assumed that chronic (*i.e.*, working lifetime) conditions apply. It is further assumed that only

adults (*i.e.,* greater than 16 years old) would be working with the degreaser, and adults (*i.e.,* greater than 16 years old) would be in the vicinity as bystanders or non-users in the workplace. Because there are both acute and chronic effects following exposure to TCE, endpoints encompassing both exposure durations were evaluated for the non-cancer risk assessment. The acute endpoints include two that are known to occur following short exposures, including neurotoxicity and developmental effects. Neurotoxicity is the basis for the identified AEGL and also is the basis for the development of occupational guidelines by OSHA and the American Conference of Governmental Industrial Hygienists (ACGIH)[21]. The developmental endpoints of concern in the inhalation studies are both increased resorptions and decreased fetal body weight. Thus, the populations of concern include both adult male (neurotoxicity) and females (neurotoxicity for non-pregnant women and developmental toxicity for women of child-bearing age). For chronic exposure concerns, the following target organs/systems have been shown to be affected in animals and/or humans following exposure to TCE: liver, kidney, immune system, male reproductive system, and cancer (*i.e.,* primarily kidney and liver, but also NHL).

For the two consumer exposure scenarios, acute exposure/effects were identified as concerns because the half-life data for TCE in humans (*i.e.,* range of values for elimination in urine after inhalation exposures is ~15 to 51 hours; see Table 3-15 and associated text) suggests that the residual TCE/metabolites from week to week for the clear protective coating spray use or for the degreaser use over two events/month, would be relatively small. Furthermore, based on the hazard endpoint, the population of concern for users of the two consumer products are adults (*i.e.,* >16 years old) and include females who are, or could possibly be, pregnant, or are of child-bearing age, and both males and females for possible neurotoxicity effects. This also means that the populations of concern for the non-user scenario also would have to be women of child-bearing age (developmental effects) and all gender/ages (neurotoxicity).

[21] The current OSHA PEL is 100 ppm and the ACGIH TLV is 25 ppm for TCE.

Table 3-20. Use Scenarios, Population of Concern, and Health Effects of Concern.

Use Scenario	Assumptions For Exposure Duration	Population of Interest	Hazard Value Used	Comments
Small commercial degreaser	Chronic exposure (2 hours per 8-hour workday, 5 days/week)	Adults (>16 years old), including women of child-bearing age	*Non-cancer*: range of hazard values for both acute and chronic effects *Cancer*: IRIS IUR	Footnotes a, b, c
Bystander to small commercial degreaser	In the same building, no direct exposure			
Hobbyist – clear protective coating spray	Acute exposure (0.5 hour/event, one event per week)	Adults (> 16 years old), including women of child-bearing age	*Non-cancer*: range of hazard values for acute effects only	Footnotes a,d
Bystander to hobbyist – clear protective coating spray	In the same building, no direct exposure	All ages		Footnotes a,d,e
Hobbyist – degreaser use	Acute (1 hour/event, two events/month)	Adults (> 16 years old), including women of child-bearing age		Footnotes a,d
Bystander to hobbyist – degreaser use	In the same building, no direct exposure	All ages		Footnotes a,d,e

[a]Acute exposure concern is for women of child-bearing age (possible developmental effects) as well as all adults for possible neurotoxicity.
[b]Possible chronic exposure concern due to effects on the liver, kidney, immune system and reproductive (male) effects.
[c]Possible cancer concern from chronic exposure (kidney, liver, NHL).
[d]Half-life in humans suggests that there would be minimal carryover exposure from week to week; thus, there is no chronic exposure concern.
[e]Acute exposure concern is for women of child-bearing age (possible developmental effects) as well as all ages for possible neurotoxicity. The neurotoxicity endpoints used were based on adult animals or humans; thus, there is some uncertainty about their applicability to younger ages which are included in the consumer bystander scenario.

Acute or chronic MOEs (MOE_{acute} or $MOE_{chronic}$) are used in this assessment to estimate non-cancer risks:

$$\mathbf{MOE_{acute\ or\ chronic}} = \frac{\textbf{Hazard value (POD)}}{\textbf{Exposure value}}$$

MOE = margin of exposure (unitless)
Hazard value (POD) = point of departure for hazard endpoint (ppm)

Exposure value = Exposure (in ppm)

Benchmark MOE values generally range between 10 and 100, depending on the endpoint, the population being evaluated, and a number of other factors generally associated with uncertainty. Generally, each order of magnitude (*i.e.*, factor of 10) is used to represent some uncertainty, such as in extrapolating data from animal studies to humans, from one route of exposure to another, for intraspecies differences within the human population, or extrapolation based on exposure duration of the study (*i.e.*, from short- to longer-term). In this case, all of the PODs were derived using a PBPK model to extrapolate an internal dose in the animal to an internal dose in humans (HEC). In addition, the HECs derived were presented both in terms of median (HEC_{50}) and 99^{th} percentile (HEC_{99}) predictions.

If MOEs are less than the benchmark MOE value, there could be a cause for concern, depending upon the frequency of such exposures and their magnitude. Thus, in this assessment, because the HEC_{99} is more conservative, a benchmark MOE will be 30 (*i.e.,* based on a factor of 10 for intraspecies variability and uncertainty and a factor of 3 for the pharmacodynamic portion of the interspecies extrapolation factor; the latter being reduced based on the kinetic modeling performed to arrive at an HEC).

The equation for cancer risk estimation is presented below. Estimates of cancer risks should be interpreted as the incremental probability of an individual developing cancer over a lifetime as a result of exposure to the potential carcinogen (*i.e.*, incremental or excess individual lifetime cancer risk).

Risk = Human Exposure × IUR

Risk = cancer risk (unitless)
Human exposure = human exposure estimate ($\mu g/m^3$)
IUR = inhalation unit risk (4.1×10^{-6} per $\mu g/m^3$) [22]

Risk Estimates for Acute (Short-Term) and Chronic (Repeated) Exposures to TCE

Small Commercial Degreaser Scenario

Table 3-21 presents the results of calculating the non-cancer risk estimate for the small commercial degreaser exposed to TCE using the MOE method. Calculations were made for different exposure scenarios (*i.e.,* acute and chronic, user and bystander, with and without LEV). Six different hazard endpoints were evaluated and for each one the lowest HEC_{99} was used from among the available inhalation studies (see Table 3-17).

[22] The IUR is 4.1×10^{-6} per $\mu g/m^3$; which converts to 4.1×10^{-6} per 0.2 ppb (or 0.0002 ppm), which in turn is $(4.1 \times 10^{-6})(5{,}000)$ [conversion factor to make the unit risk per ppm for ease in calculation) = 2×10^{-2} per ppm.

The results show that there are potential non-cancer risk concerns for all endpoints and for both acute and chronic exposure conditions when the lowest HEC_{99} POD is used. Table 3-19 also presents a higher HEC_{99} POD value as well as a range of HEC_{50} values. If these values are used, there would be changes in some scenarios (*i.e.,* see summary at the end of this section and Table 3-26). Though there is a wide range of POD values for different inhalation endpoints, the results suggest an important point about the relative sensitivity of different organ systems. For TCE, the most sensitive endpoints appear to be developmental toxicity and toxicity to the kidney and immune system; neurotoxicity and reproductive toxicity are estimated to be 10 times less sensitive, whereas liver toxicity is approximately 100 times less sensitive than those endpoints.

Table 3-22 presents the excess lifetime cancer risk to TCE using the exposure assumptions identified previously and the US EPA (2011c) IRIS IUR value for cancer potency for the small commercial degreaser/bystander exposure scenarios. The values indicate that all estimated cancer risks are above concern levels for either the occupational setting (1×10^{-5}) or the general population (1×10^{-6}). Again, the non-users represent individuals who are nearby where the actual work is being done, but are not directly involved in use of product.

Table 3-21. TCE Noncancer Risk Estimates for Small Commercial Degreasers and Non-users: Using the Lowest 99th Percentile HECs (Numbers are MOEs)[1,2]

Exposure Duration	Hazard Value[2]	Exposure Values[4] ↓ → Endpoint of Concern	Degreaser Worker				Degreaser Bystander			
			With LEV[3]		Without LEV		With LEV		Without LEV	
			Typical	Worst-Case	Typical	Worst-Case	Typcial	Worst-Case	Typical	Worst-Case
			2 ppm	6 ppm	17 ppm	63 ppm	1 ppm	5 ppm	9 ppm	55 ppm
Acute	4.8	Neurotoxicity	**2.4**	**0.8**	**0.3**	**0.08**	**4.8**	**1.0**	**0.5**	**0.09**
	6.2	Developmental Toxicity	**3.1**	**1.0**	**0.4**	**0.1**	**6.2**	**1.2**	**0.7**	**0.1**
Chronic	9.1	Liver	**4.6**	**1.5**	**0.5**	**0.1**	**9.1**	**1.8**	**1.0**	**0.2**
	0.013	Kidney	**0.007**	**0.002**	**0.0008**	**0.0002**	**0.013**	**0.003**	**0.001**	**0.0002**
	11	Immune System	**5.5**	**1.8**	**0.6**	**0.2**	**11**	**2.2**	**1.2**	**0.2**
	0.5	Male Reproductive System	**0.3**	**0.08**	**0.03**	**0.008**	**0.5**	**0.1**	**0.06**	**0.009**

1 All values are rounded for simplicity. See text for further explanation about MOEs; all bolded values are considered to represent potential risk concern.

2 All values are in ppm and represent the lowest HEC_{99} from an inhalation study for the endpoint listed.

3 LEV = local exhaust ventilation

4 The two numbers represent typical and worst case as 8 hour TWA in ppm. See text under *Exposure Assessment* for details

Table 3-22. TCE Cancer Risk Estimates for Small Commercial Degreasers and Non-users (Numbers are Extra Lifetime Cancer Risk and Bolded Vales Represent Concern

	Typical Exposure Values[a]				Worst-Case Exposure Values[a]			
	Degreaser (Inhalation)		Degreaser Bystander (Inhalation)		Degreaser (Inhalation)		Degreaser Bystander (Inhalation)	
	With LEV	Without LEV	With LEV	Without LEV	With LEV	Without LEV	With LEV	Without LEV
Estimated exposure levels (concentration in air in ppm)	2	17	1	9	6	63	5	55
Cancer risk[b]	**1.3×10^{-3}**	**$>10^{-2}$**	**6.6×10^{-4}**	**5.9×10^{-3}**	**4.0×10^{-3}**	**$>10^{-2}$**	**3.3×10^{-3}**	**$>10^{-2}$**

[a] The two numbers represent typical and worst case as 8-hour TWA in ppm. See text under *Exposure Assessment* for details.

[b] Excess lifetime cancer risk calculated as follows using California Environmental Protection Agency methodology (CalEPA, 2007):
Excess Lifetime Risk = (concentration in $\mu g/m^3$)(2 hours/24 hours)(5 days/7 days)(50 weeks/52 weeks)(40 years/ 70 years)(IUR per $\mu g/m^3$). The IUR value from US EPA (2011c) IRIS is 4.1×10^{-6} per $\mu g/m^3$, which converts to 4.1×10^{-6} per 0.2 ppb (or 0.0002 ppm) and in turn is $(4.1 \times 10^{-6})(5{,}000)$ (conversion factor to make the unit risk per ppm for ease in calculation) = 2×10^{-2} per ppm. Thus, for each exposure value above, the excess lifetime cancer risk = (exposure concentration in ppm)(0.033)(2×10^{-2} per ppm), where the 0.033 is the product of (2 hours/ 24 hours)(5 days/7days) (50 weeks/52 week) (40 years/70 years). A cell's notation that the excess lifetime cancer risk is "$>10^{-2}$" indicates that the average daily lifetime exposure is larger than the value at which the linear approximation ceases to apply (the threshold value is 15.2 ppm, which is (1×10^{-2})(IUR)).

Consumer (Hobbyist Degreaser and Arts and Crafts Clear Protective Coating Spray User)

No chronic risk concerns were identified for these scenarios, based on the following assumptions: 1) the half-life data in humans, and 2) the duration of 0.5 or one hour per event, which occurs once per week for the arts/crafts user two times per month for the consumer hobbyist degreaser use. Because only acute exposure scenarios are expected, the two endpoints of concern are neurotoxicity (both genders and all ages) and developmental toxicity (women of child-bearing age).

Table 3-23 presents the results of calculating the acute, non-cancer risk estimate for the hobbyist degreaser, arts/crafts user, and non-users exposed to TCE using the MOE method and neurotoxicity as an endpoint of concern. Results show no risk concern for non-users of the clear protective coating spray; all other scenarios show risk concerns (clear protective spray users and degreaser user and non-user).

Because the neurotoxicity endpoint of concern used to derive the POD was observed in adult animals (change in wakefulness), it is likely that the younger ages in Table 3-23 may respond differently (in terms of dose, magnitude or response, or different response). Thus, the MOEs presented in Table 3-23 may under-estimate risk to these age groups for this endpoint.

Table 3-23. TCE Non-cancer Risk Estimates for Use of Two Hobbyist Products Indoors at Residences: Neurotoxicity as Endpoint of Concern and Using the Lowest 99th Percentile HECs and 24-Hour Average Exposure Concentrations (Numbers are MOEs])[1].

Ages of Ind. (yrs)	Clear protective coating spray User	Clear protective coating spray non-user	Solvent degreaser user	Solvent degreaser non-user
	4.8[2]	4.8	4.8	4.8
<1	NA[3]	48[5]	NA	**6**[7]
1-2	NA	48	NA	**6**
3-5	NA	48	NA	**6**
6-10	NA	48	NA	**6**
11-15	NA	48	NA	**6**
16-20	**12**[4]	48	**2**[6]	**6**
> 21	**12**	48	**2**	**6**

[1]All values are rounded for simplicity. See text for further explanation about acceptable MOEs; all bolded values are considered to represent risk concerns.

[2]The lowest HEC_{99} for neurotoxicity from an inhalation study is presented (in ppm).

[3]NA = not applicable. Individuals less than 16 years old are assumed to not use either TCE-containing product.

[4]The exposure value used was 0.4 ppm

[5] The exposure value used was 0.1 ppm

[6]The exposure value used was 2 ppm

[7]The exposure value used was 0.8 ppm

Table 3-24 presents the results of calculating the acute, non-cancer risk estimate for the hobbyist degreaser, arts/crafts user, and non-users exposed to TCE using the MOE method and developmental toxicity as an endpoint of concern. For these scenarios, only women of child-bearing age are considered the population of concern. As with the neurotoxicity endpoint, results show no risk concern for non-users of the clear protective coating spray; all other scenarios show risk concerns (clear protective spray users and degreaser user and non-user.

Table 3-24. TCE Non-cancer Risk Estimates for Use of Two Hobbyist Products Indoors at Residences: Developmental Toxicity as Endpoint of Concern Using the Lowest 99th Percentile HECs and 24-Hour Average Exposure Concentrations (Numbers are MOEs)[1]

Population of Concern	Clear Protective Coating Spray User	Clear Protective Coating Spray Non-user	Solvent Degreaser User	Solvent Degreaser Non-user
	6.2[2]	6.2	6.2	6.2
Women of child-bearing age	**16**[3]	62[4]	**2**[5]	**8**[6]

[1]All values are rounded for simplicity. See text for further explanation about acceptable MOEs; all bolded values are considered to represent risk concerns.

[2]The lowest HEC_{99} for developmental toxicity from an inhalation study is presented (in ppm).

[3]The exposure value used was 0.4 ppm

[4]The exposure value used was 0.1 ppm

[5]The exposure value used was 2 ppm

[6]The exposure value used was 0.8 ppm

Summary

This risk assessment focused on three exposure scenarios for TCE: small commercial degreasing operations; consumer use of an aerosol degreaser; and the consumer use of a clear protective coating spray in an arts/crafts home setting. Assumptions and estimations on the exposure values used have been presented, and the associated uncertainties are described below. Only the inhalation route of exposure was considered in this risk assessment. Other approaches, including use of the IRIS RfC, may be appropriate for other risk assessments.

On the hazard side of the risk equation, OPPT used the literature review and analyses performed by the US EPA's IRIS program to identify 12 inhalation studies considered relevant for this particular assessment. Relevancy was primarily based on the route of exposure (inhalation). In addition, the TCE database is robust, and there is evidence for a variety of adverse effects in animals, and potentially, humans. For inhalation studies, these include effects that may be elicited following a single, or short-term exposure (*e.g.,* neurotoxicity and developmental toxicity), as well as effects associated with long-term or chronic exposures (*e.g.,* immunotoxicity, kidney toxicity, liver toxicity, reproductive effects in males and cancer [kidney, liver, and NHL).

This risk assessment, using MOEs for all non-cancer effects and the IRIS IUR for cancer effects, identified risks for virtually all scenarios (see Table 3-25).

Table 3-25. Summary of Overall Risk Assessment for TCE Using the Lowest 99th Percentile HECs

Exposure Category	Chronic Non-Cancer Risk?	Acute Non-Cancer Risk?	Cancer Risk?
Small Commercial Degreaser operator (user)	YES	YES	YES
Small Commercial Degreaser operator (non-user)	YES	YES	YES
Consumer Degreaser (user)	Not Applicable	YES	Not Applicable
Consumer Degreaser (non-user)	Not Applicable	YES	Not Applicable
Consumer Clear Protective Coating Spray (user)	Not Applicable	YES	Not Applicable
Consumer Clear Protective Coating Spray (non-user)	Not Applicable	**NO**	Not Applicable

The range of estimated exposure values for the worker and consumer scenarios are:

- Small commercial degreaser worker user: from 2-63 ppm (30× difference)
- Small commercial degreaser non-user: from 1-55 ppm (55× difference)
- Consumer degreaser user/non-user: from 0.8 - 2 ppm (~2× difference)
- Consumer clear protective coating spray user/non-user: from 0.1 - 0.4 ppm (4× difference)

The range of hazard values used in the risk assessment (using the lowest HEC_{99} value in the range reported for each major target organ/endpoint) was < 2 for the acute toxicity endpoints and almost 1,000 for the chronic toxicity endpoints:

- Acute toxicity: 4.8 – 6.2 ppm (neurotoxicity and developmental toxicity, respectively)
- Chronic toxicity: 0.013 – 9.1 ppm (for kidney and liver toxicity, respectively).

Although there may be some differences in the risk outcome if alternate exposure values were available, given the ranges seen (*i.e.,* 55x being the highest), this difference is only slightly higher than an order of magnitude. However, there are many different hazard values that could also be used and, if used, would likely present a different risk profile for the scenarios that are the focus of this assessment.

Although not presented quantitatively, Table 3-26 presents the results of the risk assessment if different HEC values were used. In Table 3-19, in order to provide an indication of the variability in the HEC predictions, the range of hazard values for the "typical" human (the 50th percentile or HEC_{50}) is also presented. As explained earlier, the terms "low-end" and "high-end" represent the minimum and maximum values for the data sets within each major target organ/endpoint. Thus, if one were to take three other sets of hazard values (the high-end HEC_{99}, the low-end

HEC_{50}, and the high-end HEC_{50}), the qualitative results are presented in Table 3-26. Examples for each "alternate" hazard value used are presented below:

- The high-end HEC_{99} value in the range reported in Table 3-19 for each target organ/endpoint (*i.e.,* the 99th percentile represents a "sensitive" human HEC; an example value is 19 ppm for the liver [the low-end HEC_{99} used in Tables 3-20 was 9.1 ppm]).
- The low-end HEC_{50} value in the range reported in Table 3-19 for each target organ/endpoint (*i.e.,* the 50th percentile represents a "typical" human HEC; an example value is 25 ppm for the liver).
- The high-end HEC_{50} value in the range reported in Table 3-19 for each target organ/endpoint (*i.e.,* the 50th percentile represents a "typical" human HEC; an example value is 53 ppm for the liver).

Though complicated given all the permutations[23], EPA draws some generalizations, including:

- If evaluated by "typical" or "sensitive" HEC:
  - The lower-end HEC_{50} shows risk for all scenarios/endpoints except for the acute clear protective coating spray user and non-user scenarios;
  - The higher-end HEC_{50} and higher-end HEC_{99} values show no risk concern for some scenarios (see Table 3-26) and some endpoints (reproductive toxicity, immunotoxicity, and liver toxicity)
- If evaluated by user/non-user scenario:
  - If any of the three alternate HEC values listed above is used (except for developmental toxicity for the higher-end HEC_{99} value) for the clear protective coating spray user/non-user scenario, there is no risk concern
- If evaluated by acute effect endpoint:
  - Risk concern for neurotoxicity does change from "risk" to "no risk" for all scenarios except for the worker and consumer degreaser when the lower-end HEC_{50} is used
- If evaluated by chronic effect endpoint:
  - There is no change in risk estimates for kidney effects regardless of the HEC value used
  - Some risk concerns are alleviated depending on the HEC value used for reproductive toxicity and immunotoxicity, and, to a lesser extent, liver toxicity

Even with these alternative analyses, the results suggest concern for most scenarios that were the focus of this risk assessment except perhaps for the clear protective coating spray in the case of non-users. In terms of acute effects, neurotoxicity seems less of a concern than

[23] Four different hazard values (the lowest HEC_{99}; the primary value used in this risk assessment) plus three other measures as shown in Table 3-19. Especially for the worker scenario: typical vs. worst-case, with and without LEV, user and non-user, two acute endpoints and four chronic endpoints. For the consumer scenarios it is less complicated (user and non-user).

developmental toxicity. For the chronic effect endpoints, the kidney hazard value appears to be the predominant concern regardless of HEC value chosen (*i.e.*, kidney toxicity seems to be the most sensitive chronic endpoint).

In terms of cancer risk assessment, use of the IRIS IUR suggests risk to workers/non-users regardless of their potential exposure (*i.e.,* from a low of 1 ppm up to the highest exposure estimate of 63 ppm).

Table 3-26. Changes in the Non-Cancer MOEs If Different HECs are Used [a]

Exposure Category	Change in Chronic Risk With…			Change in Acute Risk With…		
	Higher-End HEC_{99}	**Lower-End HEC_{50}**	**Higher-End HEC_{50}**	**Higher-End HEC_{99}**	**Lower-End HEC_{50}**	**Higher-End HEC_{50}**
Small Commercial Degreaser operator (user)	**YES[b]**	NO[b]	**YES -**	**YES**	NO	**YES**
Small Commercial Degreaser operator (non-user)	**YES**	NO	**YES**	**YES**	NO	**YES**
Consumer Degreaser (user)	Not Applicable (N/A)			**YES**	NO	**YES**
Consumer Degreaser (non-user)				**YES**	NO	**YES**
Consumer Clear Protective Coating Spray (user)				**YES**	**YES**	**YES**
Consumer Clear Protective Coating Spray (non-user)				NO	NO	NO

[a] HEC_{50} represents the typical human HEC; HEC_{99} represents the sensitive human HEC. the terms "low-end" and "high-end" represent the minimum and maximum values for the data presented in Table 3-19. Changes are meant to be from the non-cancer MOEs listed in Tables 3-21, 3-23 and 3-24.

[b] In general, a "YES" means a change in one or more risk values from "potential risk" to "no risk". A "NO" means there were no changes from the risk assessment as presented in the main body of this risk assessment.

D. Discussion of Key Sources of Uncertainty and Data Limitations

Uncertainties in the Exposure Assessment

The production volume and release information on TCE are estimates, actual TCE production or import into the US may differ from these estimates. The 2011 production volume and use data reported here (Glauser and Funda, 2012) are recent and considered reliable. It seems clear that the vast majority of the TCE used in the US is as an intermediate for the production of a refrigerant and the second highest use (in terms of production volume) is as a degreaser. Confidence in the remaining uses (*i.e.*, <2 percent of the production volume) is less certain.

For small commercial/industrial degreasing facilities, environmental releases of and workplace exposures to TCE were estimated based on several data sources (*i.e.,* NAICS, NEI, and TRI). Further, certain assumptions were made in developing these estimates (*e.g.*, effectiveness of workplace controls, operating hours, number of workers per facility, the number of small commercial/industrial facilities) and various "what-if" scenarios were evaluated to quantify "typical" and "worst-case" workplace exposure estimates. Though the uncertainty in these assumptions was not extensively evaluated, EPA did compare its release and exposure estimates to values in the literature; EPA estimates and literature values were of the same order of magnitude. For the purposes of this assessment, "typical" and "worst-case" estimates represent exposure values to which workers are likely exposed to during (1) routine working conditions, and (2) non-routine (episodic) working conditions, respectively.

Although TCE products intended for use by consumers were found by EPA, there is some uncertainty in terms of the nature and extent of the consumer use of TCE in general. Furthermore, for the exposure estimations in this risk assessment, the use patterns assumed for the two hobbyist products, including mass of product used per event, duration of event, and events per year, are hypothetical and are not based on consumer product survey data. Therefore, they are likely the source of the greatest uncertainties/data gaps in the exposure estimates for the two hobbyist products. However, there is a high degree of confidence in the consumer product weight fractions identified for the two hobbyist products evaluated in this assessment. Also, there is a medium to high degree of confidence in certain modeling inputs to the E-FAST/CEM model, including vapor pressure, molecular weight, room volumes, whole house volume, air exchange rate, body weight, and inhalation rate.

Because the E-FAST2/CEM model outputs for exposure to the user and non-user hobbyist scenarios are reported in mg/kg-bw/day, it was necessary to convert these values to air concentrations (ppm) in order to perform the non-cancer and cancer risk assessment. This conversion introduces some uncertainty, but it is not apparent whether it may over- or under-estimate exposures.

Finally, although it was assumed that dermal exposure to the TCE use scenarios was less significant compared with the inhalation exposure, EPA expects dermal exposures under some

conditions. Thus, total exposure may be underestimated because combining dermal and inhalation exposures was not done in this risk assessment. This would likely be an issue of concern in those exposure scenarios which resulted in a "no-risk" finding. Additional exposure *via* the dermal route could lead to an alternative risk finding. However, use of the lower-end HEC_{99} value for hazard – which represents a sensitive human HEC – does provide a certain amount of conservatism that can provide a counterweight to not considering dermal exposure.

Uncertainties in the Hazard Assessment

The hazard information available on TCE is quite large and includes many studies with both humans and animals. Virtually all of the information on TCE hazard for this risk assessment was taken from the recent IRIS publication (US EPA, 2011c), in which dozens of pages are devoted to discussions of uncertainty throughout the document[24]. Only the uncertainties germane to the specifics of this risk assessment are discussed.

In developing an RfC or RfD, uncertainty is captured by the use of uncertainty factors (UFs). Depending on the POD, UFs of between 10 and 1,000 were used to derive candidate RfD/RfCs. In this risk assessment, rather than using a single value (*i.e.*, the RfC) to evaluate inhalation exposures for the scenarios identified, it was decided to evaluate the range of data evaluated by the IRIS program to derive the RfC. This resulted in the identification of 32 PODs from 27 studies for use in the non-cancer risk assessment; of which 17 PODs from 12 inhalation studies were chosen and from which six hazard values were identified for use in this risk assessment. The PODs covered both acute (*i.e.,* neurotoxicity and developmental toxicity) and chronic (*i.e.,* liver, kidney, immunotoxicity, reproductive toxicity) endpoints. For the cancer risk assessment, the IRIS IUR was used.

The use of PODs for each major adverse effect, adds a level of confidence to the hazard and risk assessment. Because the database for TCE exposures to animals and humans is very robust, using specific adverse effects with the appropriate exposure scenarios raises the confidence that the risk estimations are relevant for real world exposures.

As pointed out in the IRIS Toxicological Review (US EPA, 2011c), there is uncertainty associated with each POD.[25] In this risk assessment, these individual UFs may be minimized given that EPA used a maximum value for each endpoint type for the inhalation studies used in our analysis. By focusing only on inhalation studies and using lower-end HEC_{99} values, OPPT has increased

[24]For example, the confidence pertaining to the knowledge of the metabolism of TCE in both animals and humans will not be discussed here. The PBPK model developed for TCE tries to take this into account. Associated with the metabolism issue is the uncertainty of extrapolating from one route of exposure to another; which is one reason why OPPT chose to use only the inhalation studies identified by IRIS.

[25] UFs = uncertainty factors; UF_L = uncertainty in extrapolating from a LOAEL to a NOAEL; UF_A = uncertainty in extrapolating from animals to humans ("interspecies UF"); UF_H = uncertainty to address variation in human susceptibility ("intraspecies UF"); UF_s = uncertainty in extrapolating data from less-than lifetime studies; UF_D = uncertainty due to incomplete database.

the likelihood that risks are not under-estimated. Furthermore, use of the lower-end HEC for the 99th percentile, although conservative, presents an interesting picture of the likely hazard of TCE. As seen below, there is an approximate1000-fold difference between the lowest (0.013 ppm) and highest (11 ppm) lower-end HEC_{99}:

- Neurotoxicity = 4.8 ppm
- Developmental Toxicity = 6.2 ppm
- Liver toxicity = 9.1 ppm
- Kidney toxicity = 0.013 ppm
- Immune system =11 ppm
- Male reproductive toxicity = 0.5 ppm

By choosing only one of these values (*e.g.,* the lowest), the risk picture would be quite different than if another (*e.g.,* the highest) single value is used; there is a 1000-fold difference between these two values. However, by presenting all six endpoints in the context of the exposure duration of concern, a "full" hazard/risk picture is observed.

As shown in Table 3-26, using different HEC_{50} and HEC_{99} values does change the risk picture somewhat for some exposure scenarios; primarily eliminating acute effect risk concerns for neurotoxicity for consumer users and non-users of both the degreaser and clear protective coating spray scenarios. However, regardless of the hazard value used within the bounds identified in this assessment, chronic effects concerns continue to exist for the small commercial worker for most scenarios, and for all scenarios with kidney toxicity as the endpoint of concern.

Uncertainties in the Risk Assessment

The uncertainties discussed above for both the exposure and hazard portions of this risk assessment can be discussed in a qualitative manner. First, the range of values in the exposure estimations for the worker and consumer scenarios is not large. Including all scenarios for users and non-users, the range in exposure values for the worker (1 to 63 ppm), and the two consumer uses (0.1 to 2 ppm) is between 60 and 20 fold, respectively. The hazard values (*i.e.,* using the lowest HEC_{99} values) ranged from <2 to almost 1,000 for the acute toxicity endpoints and for the chronic toxicity endpoints, respectively:

- Acute toxicity: 4.8 to 6.2 ppm (neurotoxicity and developmental toxicity, respectively)
- Chronic toxicity: 0.013 to 9.1 ppm (for kidney and liver toxicity, respectively).

Thus, understanding that the exposure estimates may be an over- or under-estimation, the choice in the hazard value used will likely have a greater influence on the outcome of the risk assessment for the uses discussed in this risk assessment.

CONCLUSIONS

TCE is a volatile organic compound that is produced/imported into the US in large quantities (*i.e.,* >250 million lbs per year), the majority (~85 percent) of which is used as an intermediate chemical for manufacturing refrigerant chemicals. Much of the remainder (*i.e.,* ~15 percent) is used as a solvent for metals degreasing. A relatively small percentage (*i.e.,* ~2 percent) is used in a variety of applications, including as a solvent for metal degreasing by consumers who work on their own cars, bikes, *etc.* (*i.e.*, DIY hobbyists) and as an ingredient in other hobbyist products, including a clear protective coating spray used in the arts/crafts field, a film cleaner, a toner aide, and a mirror edge sealant. EPA's assessment focused on uses of TCE as a degreaser both in small commercial settings and consumers, and the consumer use of TCE in a clear protective coating spray by individuals in the arts/crafts field.

The results of this risk assessment indicate possible acute and chronic non-cancer risk concerns for occupational (*i.e.,* small commercial settings) degreasers and bystanders (non-users). There are also cancer risk concerns for this population:

- For the commercial degreaser user and non-user, non-cancer MOEs were less than 30 (potential risk concern) for acute toxicity effects (*i.e.,* developmental toxicity and neurotoxicity) and chronic effects (*i.e.,* liver, kidney, and immune system effects).

- For the commercial degreaser user and non-user, using the IRIS IUR, the cancer risks were all below the benchmark value (*i.e.,* potential risk concern).

Results of evaluating the two consumer use products suggest acute, non-cancer risks to users of both types of products for both developmental toxicity and neurotoxicity. For non-users, EPA's analysis suggests there is potential concern for the degreaser exposure scenario (for both developmental toxicity and neurotoxicity); whereas no concern was identified for either effect for the clear protective spray non-user scenario:

- For the hobbyist degreaser user and non-user and for the hobbyist clear protective spray users, the acute, non-cancer MOEs for developmental toxicity were less than 30 (potential risk concern).

- The hobbyist clear protective spray non-user scenario resulted in an MOE of greater than 30 (no risk concern) for both developmental toxicity and neurotoxicity

The use of the consumer products is infrequent, and thus, EPA did not conduct either a chronic non-cancer or cancer risk assessment for these use scenarios.

References

Arif, A., and Shah, S. (2007). Association between personal exposure to volatile organic compounds and asthma among US adult population. *Int. Arch. Occup. Environ. Health* **80**, 711-719.

Arito, H., Takahashi, M., and Ishikawa, T. (1994). Effect of subchronic inhalation exposure to low-level trichloroethylene on heart rate and wakefulness-sleep in freely moving rats. *J. Occup. Health* **36**, 1-8. (as cited in US EPA, 2011c).

Arkema (2011). Material Safety Data Sheet. Trichloroethylene. Arkema Inc. http://www.arkema-inc.com/msds.cfm. Accessed August 17, 2012.

Ash, M., and Ash, I. (2009). 1,1,2-Trichloroethylene. In *Handbook of Industrial Chemical Additives. Second edition, Volume II.* Synapse Information Resources.

ATSDR (1997). Toxicological profile for trichloroethylene. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp19.pdf. Accessed September 6, 2012.

ATSDR (1999). Update on the status of the Superfund Substance-specific Applied Research Program. Agency for Toxic Substances and Disease Registry. *Fed. Regist.* **64**(10), 2760-2790. http://www.gpo.gov/fdsys/pkg/FR-1999-01-15/pdf/99-971.pdf. Accessed August 17, 2012.

ATSDR (2011). Priority list of hazardous substances. Agency for Toxic Substances and Disease Registry, Atlanta, GA. http://www.atsdr.cdc.gov/SPL/. Accessed November 6, 2012.

Baldwin, P. E., and Maynard, A. D. (1998). A survey of wind speeds in indoor workplaces. *Ann. Occup. Hyg.* **42**(5), 303-313.

Bartonicek, V. (1962). Metabolism and excretion of trichloroethylene after inhalation by human subjects. *Occup. Environ. Med.* **19**, 134-141. (as cited in US EPA, 2011c).

Buben, J., and O'Flaherty, E. (1985). Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: A dose-effect study. *Toxicol. Appl. Pharmacol.* **78**, 105-122. (as cited in US EPA, 2011c).

CalEPA (2007). Occupational health hazard risk assessment: Project for California: Identification of chemicals of concern, possible risk assessment methods, and examples of health protective occupational air concentrations. California Environmental Protection Agency. www.cdph.ca.gov/programs/hesis/Documents/riskreport.pdf. Accessed November 6, 2012.

Chia, S., Ong, C., Tsakok, M., and Ho, A. (1996). Semen parameters in workers exposed to trichloroethylene. *Reprod. Toxicol.* **10**, 295-299. (as cited in US EPA, 2011c).

Chiu, W., Micallef, S., Monster, A., and Bois, F. (2007). Toxicokinetics of inhaled trichloroethylene and tetrachloroethylene in humans at 1 ppm: Empirical results and comparisons with previous studies. *Toxicol. Sci.* **95**, 23-36.

Chiu, W. A., Okino, M. S., and Evans, M. V. (2009). Characterizing uncertainty and population variability in the toxicokinetics of trichloroethylene and metabolites in mice, rats, and humans using an updated database, physiologically based pharmacokinetic (PBPK) model, and Bayesian approach. *Toxicol. Appl. Pharmacol.* **241**(1), 36-60.

Daubert, T. E., and Danner, R. P. (1989). *Physical and thermodynamic properties of pure chemicals: Data compilation. Design Institute for Physical Property Data, American Institute of Chemical Engineers*. Hemisphere Pub. Corp., New York.

Dekant, W., Metzler, M., and Henschler, D. (1984). Novel metabolites of trichloroethylene through dechlorination reactions in rats, mice and humans. *Biochem. Pharmacol.* **33**, 2021-2027. (as cited in US EPA, 2011c).

Dilling, W. L., Tefertiller, N. B., and Kallos, G. J. (1975). Evaporation rates and reactivities of methylene chloride, chloroform, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, and other chlorinated compounds in dilute aqueous solutions. *Environ. Sci. Technol.* **9**(9), 833-838.

DuTeaux, S., Berger, T., Hess, R., Sartini, B., and Miller, M. (2004). Male reproductive toxicity of trichloroethylene: Sperm protein oxidation and decreased fertilizing ability. *Biol. Reprod.* **70**, 1518-1526. (as cited in US EPA, 2011c).

EC (2000). IUCLID Dataset for trichloroethylene. European Chemical Substances Information System (ESIS). European Commission, Joint Research Centre. Institute for Health and Consumer Protection (IHCP), European Chemicals Bureau. http://esis.jrc.ec.europa.eu/doc/IUCLID/data_sheets/79016.pdf. Accessed November 7, 2012.

EC (2004). European Union Risk Assessment Report: Trichloroethylene. Cas No: 79-01-6. EINECS No: 201-167-4. 1st Priority List, Vol. 31 European Commission, Joint Research Center. Institute for Health and Consumer Protection, European Chemicals Bureau. . EUR 21057 EN.

Evans, M. V., Chiu, W. A., Okino, M. S., and Caldwell, J. C. (2009). Development of an updated PBPK model for trichloroethylene and metabolites in mice, and its application to discern the role of oxidative metabolism in TCE-induced hepatomegaly. *Toxicol. Appl. Pharmacol.* **236**(3), 329-340.

Ferguson, R. K., and Vernon, R. J. (1970). Trichloroethylene in combination with CNS drugs. Effects on visual-motor tests. *Arch. Environ. Health* **20**, 462-467. (as cited in US EPA, 2008a).

Fogel, M. M., Taddeo, A. R., and Fogel, S. (1986). Biodegradation of chlorinated ethenes by a methane-utilizing mixed culture. *Appl. Environ. Microbiol.* **51**(4), 720-724.

Forand, S.P., Lewis-Michi, E.L., and Gomez, M.I., (2012). Adverse birth outcomes and maternal exposure to trichloroethlene and tetracholorethylene throuh soil vapor intrusion in New York state. *Environmental Health Perspectives* **120** (4), 616-621

Forkert, P., Lash, L., Nadeua, V., Tardif, R., and Simmonds, A. (2002). Metabolism and toxicity of trichloroethylene in epididymis and testis. *Toxicol. Appl. Pharmacol.* **182**, 244-254. (as cited in US EPA, 2011c).

Fredriksson, A., Danielsson, B., and Eriksson, P. (1993). Altered behaviour in adult mice orally exposed to tri- and tetrachloroethylene as neonates. *Toxicol. Lett.* **66**, 13-19. (as cited in US EPA, 2011c).

Gash, D., Rutland, K., Hudson, N., Sullivan, P., Bing, G., Cass, W., Pandya, J., Liu, M., Choi, D., Hunter, R., Gerhardt, G., Smith, C., Slevin, J., and Prince, T. (2008). Trichloroethylene: Parkinsonism and complex 1 mitochondrial neurotoxicity. *Ann. Neurol.* **63**, 184-192. (as cited in US EPA, 2011c).

Gay, B. W., Hanst, P. L., Bufalini, J. J., and Noonan, R. C. (1976). Atmospheric oxidation of chlorinated ethylenes. *Environ. Sci. Technol.* **10**(1), 58-67.

Glauser, J., and Funda, C. (2012). CEH marketing research report: C2 chlorinated solvents. In *Chemical Economics Handbook.*

Green, T., and Prout, M. (1985). Species differences in response to trichloroethylene: II. Biotransformation in rats and mice. *Toxicol. Appl. Pharmacol.* **79**, 401-411. (as cited in US EPA, 2011c).

Healy, T., Poole, T., and Hopper, A. (1982). Rat fetal development and maternal exposure to trichloroethylene 100 ppm. *Br. J. Anaesth.* **54**, 337-341. (as cited in US EPA, 2011c).

HSDB (2012). Trichloroethylene. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov/. Accessed August 15, 2012.

Iavicoli, I., Marinaccio, A., and Carelli, G. (2005). Effects of occupational trichloroethylene exposure on cytokine levels in workers. *J. Occup. Environ. Hyg* **47**, 453-457. (as cited in US EPA, 2011c).

ICIS (2010). Inorganics news in brief, October 25, 2010. ICIS Chemical Business Magazine. Reed Business Information Limited. http://www.icis.com/Articles/2010/10/25/9403851/inorganics-news-in-brief.html. Accessed November 6, 2012.

ICIS (2012). Inorganics news in brief, January 23, 2012. ICIS Chemical Business Magazine. Reed Business Information Limited.

Ikeda, M. (1977). Metabolism of trichloroethylene and tetrachloroethylene in human subjects. *Environ. Health. Perspect.* **21**, 239-245. (as cited in US EPA, 2011c).

Ikeda, M., and Imamura, T. (1973). Biological half-life of trichloroethylene and tetrachloroethylene in human subjects. *Int. Arch. Occup. Environ. Health* **31**, 209-224. (as cited in US EPA, 2011c).

IOM (2003). Gulf War and health: Volume 2. Insecticides and solvents. Committee on Gulf War and health: Literature review of pesticides and solvents. Institute of Medicine of the National Academies, National Academy of Sciences. National Academies Press, Washington, DC. http://www.nap.edu/catalog.php?record_id=10628. Accessed September 6, 2012.

Isaacson, L., Spohler, S., and Taylor, D. (1990). Trichloroethylene affects learning and decreases myelin in the rat hippocampus. *Neurotoxicol. Teratol.* **12**, 375-381. (as cited in US EPA, 2011c).

Johnson, P. D., Dawson, B. V., and Goldberg, S. J. (1998). A review: Trichloroethylene metabolites: Potential cardiac teratogens. *Environ. Health. Perspect.* **106** (Suppl 4), 995-999.

Johnson, P. D., Goldberg, S. J., Mays, M. Z., and Dawson, B. V. (2003). Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. *Environ. Health. Perspect.* **111**(3), 289-292. (as cited in US EPA, 2011c).

Jollow, D. J., Bruckner, J. V., McMillan, D. C., Fisher, J. W., Hoel, D. G., and Mohr, L. C. (2009). Trichloroethylene risk assessment: a review and commentary. *Crit. Rev. Toxicol.* **39**(9), 782-797.

Kan, F., Forkert, P., and Wade, M. (2007). Trichloroethylene exposure elicits damage in epididymal epithelium and spermatozoa in mice. *Histol. Histopathol.* **22**, 977-988. (as cited in US EPA, 2011c).

Kaneko, T., Saegusa, M., Tasaka, K., and Sato, A. (2000). Immunotoxicity of trichloroethylene: A study with MRL-lpr/lpr mice. *J. Appl. Toxicol.* **20**, 471-475. (as cited in US EPA, 2011c).

Kao, A. S. (1994). Formation and removal reactions of hazardous air pollutants. *J. Air Waste Manage. Assoc.* **44**, 683-696.

Kao, C. M., and Prosser, J. (1999). Intrinsic bioremediation of trichloroethylene and chlorobenzene: field and laboratory studies. *J. Hazard. Mater.* **69**(1), 67-79.

Keil, D. E., Peden-Adams, M. M., Wallace, S., Ruiz, P., and Gilkeson, G. S. (2009). Assessment of trichloroethylene (TCE) exposure in murine strains genetically-prone and non-prone to develop autoimmune disease. *J. Environ. Sci. Health A Tox Hazard Subst Environ. Eng* **44**(5), 443-453. (as cited in US EPA, 2011c).

Kjellstrand, P., Holmquist, B., Alm, P., Kanje, M., Romare, S., Jonsson, I., Mansson, L., and Bjerkemo, M. (1983). Trichloroethylene: Further studies of the effects on body and organ weights and plasma butyrylcholinesterase activity in mice. *Acta Pharmacol. Toxicol. (Copenh)* **53**, 375-384. (as cited in US EPA, 2011c).

Kjellstrand, P., Kanje, M., and Bjerkemo, M. (1987). Regeneration of the sciatic nerve in mice and rats exposed to trichloroethylene. *Toxicol. Lett.* **38**, 187-191. (as cited in US EPA, 2011c).

Kumar, P., Prasad, A., Maji, B., Mani, U., and Dutta, K. (2001). Trichloroethylene induced testicular toxicity in rats exposed by inhalation. *Biomed. Environ. Sci.* **14**, 325-332. (as cited in US EPA, 2011c).

Kumar, P., Prasad, A., Saxena, D., Manu, U., Maji, B., and Dutta, K. (2000). Fertility and general reproduction studies in trichloroethylene exposed rats. *Indian J. Occup. Health* **43**, 117-126. (as cited in US EPA, 2011c).

Maltoni, C and Cotti, G. (1986). Results of long-term carcinogenicity bioassays of tetrachloroethylene on Sprague-Dawley rats administered by ingestion. Acta Oncol 7: 11-26 (as cited in US EPA, 2011c).

McCarty, P. L. (1996). Biotic and abiotic transformations of chlorinated solvents in ground water. In *Symposium on natural attenuation of chlorinated organics in ground water. EPA/540/R-96/509.* p. 5-9. US Environmental Protection Agency, Office of Research and Development, Washington, DC.

Mu, D. Y., and Scow, K. M. (1994). Effect of trichloroethylene (TCE) and toluene concentrations on TCE and toluene biodegradation and the population density of TCE and toluene degraders in soil. *Appl. Environ. Microbiol.* **60**(7), 2661-2665.

Nagaya, T., Ishikawa, N., Hata, H., and Otobe, T. (1993). Subclinical and reversible hepatic effects of occupational exposure to trichloroethylene. *Int. Arch. Occup. Environ. Health* **64**, 561-563. (as cited in US EPA, 2011c).

Narotsky, M., Weller, E., Chinchilli, V., and Kavlock, R. (1995). Nonadditive developmental toxicity in mixtures of trichloroethylene, di(2-ethylhexyl) phthalate, and heptachlor in a 5 x 5 x 5 design. *Toxicol. Sci.* **27**, 203-216. (as cited in US EPA, 2011c).

NAS (2006). Assessing the human health risks of trichloroethylene: Key scientific issues. National Academy of Sciences. http://www.nap.edu/openbook.php?record_id=11707&page=R1. Accessed September 6, 2012.

NAS (2009). Contaminated water supplies at Camp Lejeune: Assessing potential health effects. National Academy of Sciences. http://www.nap.edu/catalog.php?record_id=12618. Accessed August 31, 2012.

NAS (2010). Review of studies of possible toxic effects from past environmental contamination at Fort Detrick: A letter report. National Academy of Sciences, National Research Council, Washington, DC. http://www.nap.edu/catalog.php?record_id=13375. Accessed September 6, 2012.

NCI (1976). Carcinogenesis bioassay of trichloroethylene (NCI-CG-TR-2). National Cancer Institute, National Institutes of Health. US Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. (as cited in US EPA, 2011c).

Neghab, M., Qu, S., Bai, C., Caples, J., and Stacey, N. (1997). Raised concentration of serum bile acids following occupational exposure to halogenated solvents, 1,1,2-trichloro-1,2,2-trifluoroethane and trichloroethylene. *Int. Arch. Occup. Environ. Health* **70**, 187-194. (as cited in US EPA, 2011c).

NICNAS (2000). Trichloroethylene. Priority existing chemical assessment report. No. 8. National Industrial Chemicals Notification and Assessment Scheme, Australia. http://www.nicnas.gov.au/publications/car/PEC/PEC8.asp. Accessed September 6, 2012.

NITE (2012). 1,1,2-Trichloroethene. CAS No. 79-01-6. Biodegradation and bioconcentration of the existing chemical substances under the Chemical Substances Control Law. National Institute of Technology and Evaluation, Incorporated Administrative Agency. Chemical Risk Information Platform (CHRIP). http://www.safe.nite.go.jp/english/sougou/view/ComprehensiveInfoDisplay_en.faces. Accessed November 7, 2012.

Nomiyama, K., and Nomiyama, H. (1971). Metabolism of trichloroethylene in human: Sex difference in urinary excretion of trichloroacetic acid and trichloroethanol. *Int. Arch. Occup. Environ. Health* **28**, 37-48. (as cited in US EPA, 2011c).

NTP (1986). Trichloroethylene: Reproduction and fertility assessment in F344 rats when administered in the feed. (NTP-86-085). National Toxicology Program, National Institute of Environmental Health Sciences Research Triangle Park, NC. (as cited in US EPA, 2011c).

NTP (1988). Toxicology and carcinogenesis studies of trichloroethylene (CAS No. 79-01-6) in four strains of rats (ACI, August, Marshall, Osborne-Mendel) (gavage studies). National Toxicology Program. US Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (as cited in US EPA, 2011c).

O'Neil, M. J., Smith, A., and Heckelman, P. E. (2001). Trichloroethylene. In *Merck Index.* 13th ed., p. 1718. Merck & Co., Inc, Whitehouse Station, NJ.

OECD/SIDS (1996). SIDS initial assessment profile. Trichloroethylene (CAS No. 79-01-6). SIAM 4, 20-22 May 1996. Organisation for Economic Co-operation and Development, Screening Information Data Sets. United Kingdom. http://webnet.oecd.org/hpv/ui/handler.axd?id=0bd4d332-9404-4bf6-8c31-3b7aab3910bf. Accessed November 7, 2012.

Ogata, M., Takatsuka, Y., and Tomokuni, K. (1971). Excretion of organic chlorine compounds in the urine of persons exposed to vapours of trichloroethylene and tetrachloroethylene. *Occup. Environ. Med.* **28**, 386-391. (as cited in US EPA, 2011c).

Opdam, J. (1989). Intra and interindividual variability in the kinetics of a poorly and highly metabolising solvent. *Br. J. Ind. Med* **46**, 831-845. (as cited in US EPA, 2011c).

Peden-Adams, M. M., Eudaly, J. G., Heesemann, L. M., Smythe, J., Miller, J., Gilkeson, G. S., and Keil, D. E. (2006). Developmental immunotoxicity of trichloroethylene (TCE): studies in B6C3F1 mice. *J. Environ. Sci. Health A Tox Hazard Subst Environ. Eng* **41**(3), 249-271.

Prout, M., Provan, W., and Green, T. (1985). Species differences in response to trichloroethylene: I pharmacokinetics in rats and mice. *Toxicol. Appl. Pharmacol.* **79**, 389-400. (as cited in US EPA, 2011c).

Rasmussen, K., Brogren, C., and Sabroe, S. (1993). Subclinical affection of liver and kidney function and solvent exposure. *Int. Arch. Occup. Environ. Health* **64**, 445-448. (as cited in US EPA, 2011c).

Ruijten, M., Verberk, M., and Salle, H. (1991). Nerve function in workers with long term exposure to trichloroethene. *Br. J. Ind. Med* **48**, 87-92. (as cited in US EPA, 2011c).

Sanders, V., Tucker, A., White, K., Kauffman, B., Hallett, P., Carchman, R., Borzelleca, J., and Munson, A. (1982). Humoral and cell-mediated immune status in mice exposed to trichloroethylene in the drinking water. *Toxicol. Appl. Pharmacol.* **62**, 358-368. (as cited in US EPA, 2011c).

Sato, A., Nakajima, T., Fujiwara, Y., and Murayama, N. (1977). A pharmacokinetic model to study the excretion of trichloroethylene and its metabolites after an inhalation exposure. *Br. J. Ind. Med* **34**, 56-63. (as cited in US EPA, 2011c).

Shen, D. D. (2008). Toxicokinetics. In *Cassarett and Doull's toxicology: the basic science of poisons, seventh edition.* p. 305-327. McGraw Hill Medical Publishers, New York.

SRC (2012). The physical properties database (PHYSPROP). Syracuse Research Corporation, Syracuse, NY. http://www.srcinc.com/what-we-do/product.aspx?id=133; accessed on February 24, 2012.

Stewart, R., Dodd, H., Gay, H., and Erley, D. (1970). Experimental human exposure to trichloroethylene. *Arch. Environ. Health* **20**, 64-71. (as cited in US EPA, 2011c).

Taskinen, H., Anttila, A., Lindbohm, M., Sallmén, M., and Hemminki, K. (1989). Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scand. J. Work Environ. Health* **15**, 345-352. (as cited in US EPA, 2011c).

Taskinen, H., Kyyronen, P., and Hemminki, K. (1994). Laboratory work and pregnancy outcome. *J. Occup. Med.* **36**, 311-319. (as cited in US EPA, 2011c).

Taylor, D., Lagory, K., Zaccaro, D., Pfohl, R., and Laurie, R. (1985). Effect of trichloroethylene on the exploratory and locomotor activity of rats exposed during development. *Sci. Total Environ.* **47**, 415-420. (as cited in US EPA, 2011c).

TRI (2012a). Toxic Release Inventory (TRI) program. US Environmental Protection Agency, Washington, DC.http://www.epa.gov/tri/index.htm . Accessed April 30, 2012.

RI (2012b). Toxic Release Inventory (TRI) program. US Environmental Protection Agency, Washington, DC..http://www.epa.gov/tri/tridata/data/basicplus/index.html Accessed April 30, 2012.

US Census (2008). North American Industry Classification System. Introduction to NAICS. US Census. http://www.census.gov/eos/www/naics/. Accessed November 9, 2012.

US EPA (1979a). Water-related environmental fate of 129 priority pollutants. Volume II. Halogenated aliphatic hydrocarbons, halogenated ethers, monocyclic aromatics, phthalate esters, polycyclic aromatic hydrocarbons, nitrosamines, miscellaneous compounds. US Environmental Protection Agency, Washington, DC. EPA-440/4-79-029B.

US EPA (1979b). Identification of conventional pollutants, final rule. *Fed. Regist.* **44**, 44501.

US EPA (1980). Fate of toxic and hazardous materials in the air environment. US Environmental Protection Agency, Office of Research and Development, Research Triangle Park, NC. EPA-600/3-80-084.

US EPA (1982). Steam electric power generating point source category. Effluent limitations guidelines, pretreatment standards and new source performance standards. Final rule. *Fed. Regist.* **47**, 52290.

US EPA (1985a). Assessment of trichloroethylene as a potentially toxic air pollutant, proposed rule. *Fed. Regist.* **50**, 52422.

US EPA (1985b). National primary drinking water regulations. Volatile synthetic organic chemicals. Final rule. *Fed. Regist.* **50**, 46880.

US EPA (1986). Clarification and correction of previously published notice on the assessment of trichloroethylene as a potentially toxic air pollutant. Clarification and correction of previously published FR notice on trichloroethylene. *Fed. Regist.* **51**, 7714.

US EPA (1987a). National primary drinking water regulations. Synthetic organic chemicals. Monitoring for unregulated contaminants. Final rule. *Fed. Regist.* **52**, 25690.

US EPA (1987b). Organic chemicals and plastics and synthetic fibers category effluent limitations guidelines, pretreatment standards, and new source performance standards. Final rule. *Fed. Regist.* **52**, 42522.

US EPA (1988). Underground injection control program: hazardous waste disposal injection restrictions. Amendments to technical requirements for Class I hazardous waste injection wells. Additional monitoring requirements applicable to all Class I wells. Final rule. *Fed. Regist.* **53**, 28118.

US EPA (1989). Reportable quantity adjustments. Delisting of ammonium thiosulfate. Final rule. *Fed. Regist.* **54**, 33426.

US EPA (1991). Chemical engineering branch manual for the preparation of engineering assessments. US Environmental Protection Agency, Office of Toxic Substances, Cincinnati, OH.

US EPA (1992) TCE removal from contaminated soil and groundwater. EPA Groundwater Issue January 1992. EPA/540/S-92-002

US EPA (1994a). National emission standards for hazardous air pollutants for source categories. Organic hazardous air pollutants from the synthetic organic chemical manufacturing industry and other proccesses subject to the negotiated regulation for equipment leaks. Final rule. *Fed. Regist.* **59**, 19402.

US EPA (1994b). National emission standards for hazardous air pollutants: halogenated solvent cleaning. Final rule. *Fed. Regist.* **59**, 61801.

US EPA (1994c). Notice of opportunity to initiate negotiations for TSCA-Section 4. Enforceable consent agreements; solicitation of testing proposals for ATSDR chemicals. US Environmental Protection Agency. *Fed. Regist.* **59**(189). http://www.gpo.gov/fdsys/pkg/FR-1994-09-30/html/94-24250.htm. Accessed August 17, 2012.

US EPA (1995). Final water quality guidance for the Great Lakes System. Final rule. *Fed. Regist.* **60**(56), 15366-15425.

US EPA (1997). Exposure factors handbook. US Environmental Protection Agency. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12464. Accessed November

US EPA (1998a). Methods for exposure-response analysis for acute inhalation exposure to chemicals (external review draft). US Environmental Protection Agency, Washington, DC. EPA/600/R-98/051.

US EPA (1998b). Hazardous waste combustors; revised standards; final rule- Part 1: RCRA-comparable fuel exclusion; permit modifications for hazardous waste combustion units; notification of intent to comply; waste minimization and pollution prevention criteria for compliance extensions. US Environmental Protection Agency. *Fed. Regist.* **63**(118), 33782-33829. http://www.gpo.gov/fdsys/pkg/FR-1998-06-19/pdf/98-15843.pdf. Accessed August 17, 2012.

US EPA (1998c). National emission standards for hazardous air pollutants: wood furniture manufacturing operations. Final rule. *Fed. Regist.* **63**(248), 71376-71385.

US EPA (1998d). National primary drinking water regulations. Consumer confidence reports. Final rule. *Fed. Regist.* **63**, 44512-44536.

US EPA (1999). Category for persistent, bioaccumulative, and toxic new chemical substances. *Fed. Regist.* **64**(213), 60194-60204.

US EPA (2000). Voluntary Children's Chemical Evaluation Program. US Environmental Protection Agency. *Fed. Regist.* **65**(248), 81700-81718. http://www.gpo.gov/fdsys/pkg/FR-2000-12-26/pdf/00-32767.pdf. Accessed August 17, 2012.

US EPA (2001a). Draft generic scenario- use of vapor degreasers. US Environmental Protection Agency, Office of Pollution Prevention and Toxics, Chemical Engineering Branch.

US EPA (2001b). National emission standards for pharmaceuticals production. Final rule. *Fed. Regist.* **66**(149), 40121-40137.

US EPA (2002). National emission standards for hazardous air pollutants for friction materials manufacutring facilities. US Environmental Protection Agency. *Fed. Regist.* **67**(202), 64498-64512. http://www.gpo.gov/fdsys/pkg/FR-2002-10-18/pdf/02-26309.pdf. Accessed August 17, 2012.

US EPA (2003). National emission standards for hazardous pollutants; printing, coating, and dyeing of fabrics and other textiles; Final rule. US Environmental Protection Agency. *Fed. Regist.* **68**(103), 32172-32229. http://www.gpo.gov/fdsys/pkg/FR-2003-05-29/pdf/03-5738.pdf. Accessed August 17, 2012.

US EPA (2004). National emission standards for hazardous air pollutants: Organic liquids distribution (non-gasoline). US Environmental Protection Agency. *Fed. Regist.* **69**(22), 5038-5087. http://www.gpo.gov/fdsys/pkg/FR-2004-02-03/pdf/04-2227.pdf. Accessed August 17, 2012.

US EPA (2004a). Air toxics risk assessment reference library. Volume 1. Technical resource manual. US Environmental Protection Agency, Research Triangle Park. www.epa.gov/ttn/fera/risk_atra_vol1.html. Accessed September 5, 2012. EPA453K04001a.

US EPA (2006a). Risk assessment for the halogenated solvent cleaning source category. US Environmental Protection Agency. http://yosemite.epa.gov/ee/epa/ria.nsf/vwRef/A.2006.10?OpenDocument. Accessed November 8, 2012.

US EPA (2006b). Non-confidential 2006 IUR records by chemical, including manufacturing, processing and use information. US Environmental Protection Agency. http://cfpub.epa.gov/iursearch/. Accessed November 9, 2012.

US EPA (2007a). Exposure and fate assessment screening tool (E-FAST). Version 2.0. Documentation manual. US Environmental Protection Agency, Office of Pollution Prevention and Toxics Exposure Assessment Branch. www.epa.gov/oppt/exposure/pubs/efast2man.pdf. Accessed September 5, 2012.

US EPA (2007b). Economic impact analysis of the halogenated solvent cleaners residual risk standard. US Environmental Protection Agency, Research Triangle Park, NC.

http://www.epa.gov/ttnecas1/regdata/EIAs/hsceconanalysisreportfinaldraft60000.pdf. Accessed November 8, 2012. EPA452R07005.

US EPA (2007c). National air emission standards for hazardous air pollutants: Halogenated solvent cleaning. US Environmental Protection Agency. *Fed. Regist.* **72**(85), 25138-25159. http://www.gpo.gov/fdsys/pkg/FR-2007-05-03/pdf/E7-7668.pdf. Accessed August 17, 2012.

US EPA (2007d). Protection of stratospheric ozone: Listing of substitutes for ozone-depleting substances-n-propyl bromide in solvent cleaning. US Environmental Protection Agency. *Fed. Regist.* **72**(103), 30142-30167. http://www.gpo.gov/fdsys/pkg/FR-2007-05-30/pdf/E7-9707.pdf. Accessed August 20, 2012.

US EPA (2008a). Trichloroethylene (CAS Reg. No. 70-01-6). Interim acute exposure guideline levels (AEGLS). US Environmental Protection Agency. http://www.epa.gov/oppt/aegl/pubs/trichloroethylene_interim_dec_2008_v1.pdf. Accessed August 20, 2012.

US EPA (2008b). National emissions inventory data and documentation. US Environmental Protection Agency, Washington, DC. http://www.epa.gov/ttn/chief/net/2008inventory.html. Accessed August 16, 2012.

U.S. EPA. 2008c**.** 2008 National Emissions Inventory Data & Documentation. [Online] 2008 NEI v2, U.S. Environmental Protection Agency, 2008. [Cited: May 10, 2012.] http://www.epa.gov/ttn/chief/net/2008inventory.html.

US EPA (2009). National emission standards for hazardous air pollutants for chemical manufacturing area sources; Final rule. US Environmental Protection Agency. *Fed. Regist.* **74**(208), 56008-56056. http://www.gpo.gov/fdsys/pkg/FR-2009-10-29/pdf/E9-25576.pdf. Accessed August 20, 2012.

US EPA (2010). National primary drinking water regulations. Announcement of the results of EPA's review of existing drinking water standards and request for public comment and/or information on related issues. Notice, request for comments. *Fed. Regist.* **75**(59), 15500-15572.

US EPA (2011a). Letter to Lisa P. Jackon, EPA Administrator, Re: Review of EPA's draft assessment entitled "Toxicological Review of Trichloroethylene" (October 2009). US Environmental Protection Agency Science Advisory Board, Office of the Administrator, Washington, DC. EPA-SAB-11-002.

US EPA (2011b). Vocabulary catalog list detail - Integrated Risk Information System (IRIS) glossary. US Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, DC. http://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary. Accessed November 4, 2012.

US EPA (2011c). Toxicological review of trichloroethylene (CAS No. 79-01-6). In support of summary information on the Integrated Risk Information System (IRIS). US Environmental Protection Agency, Integrated Risk Information System, Washington, DC. http://www.epa.gov/iris/supdocs/0199index.html. Accessed November 7, 2012. EPA/635/R-09/011F.

US EPA (2011d). Expsoure factors handbook. Final. US Environmental Protection Agency, Washington, DC. http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252. Accessed September 5, 2012. EPA/600R-090052F.

US EPA (2011e). Toxic chemical release inventory reporting forms and instructions. Revised 2011 version. US Environmental Protections Agency. EPA260R10001.

US EPA (2012a). Estimation Programs Interface Suite for Microsoft Windows, v4.10. US Environmental Protection Agency, Washington, DC. http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm. Accessed November 7, 2012.

US EPA (2012b). AEGL program. US Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC. http://www.epa.gov/oppt/aegl/. Accessed October 30, 2012.

US EPA (2012c). TSCA work plan chemicals. US Environmental Protection Agency. http://www.epa.gov/oppt/existingchemicals/pubs/workplans.html. Accessed November 9, 2012.

Vernon, R. J., and Ferguson, R. K. (1969). Effects of trichloroethylene on visual motor performance. *Arch. Environ. Health* **18**, 894-900. (as cited in US EPA, 2008a).

Wackett, L. P., Brusseau, G. A., Householder, S. R., and Hanson, R. S. (1989). Survey of microbial oxygenases: trichloroethylene degradation by propane-oxidizing bacteria. *Appl. Environ. Microbiol.* **55**(11), 2960-2964.

Wadden, R. A., Scheff, P. A., and Franke, J. E. (1989). Emission factors for trichloroethylene vapor degreasers. *Am. Ind. Hyg. Assoc. J.* **50**(9), 496-500.

Wakeham, S. G., Davis, A. C., and Karas, J. A. (1983). Mesocosm experiments to determine the fate and persistence of volatile organic compounds in coastal seawater. *Environ. Sci. Technol.* **17**(10), 611-617.

Weast, R. C., and Selby, S. M. (1966). Ethene, trichloro-. In *CRC Handb. Chem. Phys.* 47th ed., p. C-314. The Chemical Rubber Co, Cleaveland, OH.

Wilson, J. T., and Wilson, B. H. (1985). Biotransformation of trichloroethylene in soil. *Appl. Environ. Microbiol.* **49**(1), 242-243.

Woolhiser, M., Krieger, S., Thomas, J., and Hotchkiss, J. (2006). *Trichloroethylene (TCE): Immunotoxicity potential in CD rats following a 4-week vapor inhalation exposure*. Unpublished report, Midland, MI. (as cited in US EPA, 2011c).

Xu, H., Tanphaichitr, N., Forkert, P., Anupriwan, A., Weerachatyanukul, W., Vincent, R., Leader, A., and Wade, M. (2004). Exposure to trichloroethylene and its metabolites causes impairment of sperm fertilizing ability in mice. *Toxicol. Sci.* **82**, 590-597. (as cited in US EPA, 2011c).

Xu, J. Q., Kochanek, K. D., Murphy, S. L., and Tejada-Vera, B. (2010). Deaths: Final Data for 2007. National Center for Health Statistics, Hyattsville, MD. http://www.cdc.gov/nchs/data/nvsr/nvsr58/nvsr58_19.pdf. Accessed November 9, 2012.

Xu, X., Yang, R., Wu, N., Zhong, P., Ke, Y., Zhou, L., Yuan, J., Li, G., Huang, H., and Wu, B. (2009). Severe hypersensitivity dermatitis and liver dysfunction induced by occupational exposure to trichloroethylene. *Ind. Health* **47**, 107-112. (as cited in US EPA, 2011c).

Appendices

Appendix A: Regulatory History of TCE at the US EPA

The purpose of this section is to provide a brief regulatory history of TCE from the perspective of the EPA. TCE has been subject to 25 final rules and notices issued by the Agency from 1979 to 2009 that were relevant or significant with regard to TCE. These 25 rules and notices were promulgated by EPA's OAR, OPPT, OSWER, and OW.

OW initially identified TCE as a "toxic pollutant" in 1979 (US EPA, 1979b). TCE was classified as a "priority pollutant" in 1982 and no discharges of TCE were allowed from steam electric power generating point sources (US EPA, 1982). OW then established a non-enforceable maximum contaminant level goal (MCLG) of 0 mg/L for TCE in 1985 (US EPA, 1985b). Two years later, OW set a maximum contaminant level (MCL) of 0.005 mg/L for drinking water (US EPA, 1987a) and set an effluent limitation of 69 µg/L maximum per day and 26 µg/L maximum per month average for new and existing sources discharging to POTWs from the organic chemicals, plastics, and synthetic fibers industrial category (US EPA, 1987b). The following year, 1988, OW prohibited injection of TCE into class I underground injection wells (US EPA, 1988). TCE was identified by OW as a bioaccumulative chemical of concern pollutant in 1995 for a final water quality guidance for the great lakes system. This established water quality criteria for protection of human health by setting a human cancer value (HCV) of 29 µg/L for drinking water and 370 µg/L for non-drinking water for the Great Lakes system (US EPA, 1995). Then, in 1998, OW identified TCE as a possible human carcinogen by establishing a national primary drinking water regulation that specified the following consumer confidence report health effect language: "some people who drink water containing trichloroethylene in excess of the MCL [0.005 mg/L] over many years could experience problems with their liver and may have an increased risk of getting cancer" (US EPA, 1998d). OW identified TCE's major sources in drinking water originating from "discharge from metal degreasing sites and other factories (US EPA, 1998d)." OW is currently evaluating and revising TCE's MCL based upon analytical feasibility (US EPA, 2010).

OAR has listed TCE as a HAP from several different industrial emission sources in multiple rules (US EPA, 1985a, 1986, 1994b, 1998c, 2001b, 2002, 2003, 2004, 2007c, 2009) as well as a "probable or possible human carcinogen" from operations including printing, coating, and dyeing of fabrics and other textiles (US EPA, 2003). OAR classified TCE as a group I chemical for emission standards for equipment leaks in the synthetic organic chemical manufacturing industry (US EPA, 1994a). In addition, OAR identified TCE as a substitute for two ozone depleting chemicals, methyl chloroform and CFC–113, for metals, electronics, and precision cleaning, in 2007 (US EPA, 2007d).

OSWER set a reportable quantity of 100 lbs (45.4 kg) for releases of TCE from vessels or facilities in 1989 (US EPA, 1989). OSWER also set a minimum required detection limit for TCE of 37 mg/kg for hazardous waste combustors in 1998 (US EPA, 1998b).

Although OPPT has only issued two notices relevant to TCE (US EPA, 1994c, 2000), other voluntary information collection activities for TCE have occurred in the past. These activities were primarily the result of two separate but related voluntary information collection activities: data gaps identified by ATSDR (US EPA, 1994c) and data gaps identified for pilot chemicals for EPA's Voluntary Children's Chemical Evaluation Program (VCCEP) (US EPA, 2000).

EPA published a notice for voluntary solicitation of testing proposals in order to be considered for an enforceable consent agreement (ECA) negotiation in 1994 for 12 substances, including TCE (US EPA, 1994c). This notice was based on data gaps identified by ATSDR in coordination with EPA. After ATSDR updated its data needs for TCE in 1999 (ATSDR, 1999), the Halogenated Solvents Industry Alliance, Inc. (HSIA) responded with its intent to fulfill four of seven identified data needs. These four data needs included developmental neurotoxicity, developmental toxicity, immunotoxicity, and neurotoxicity *via* the oral route. HSIA entered into a memorandum of understanding (MOU) with ATSDR in June of 2001 to fulfill these four data needs.

Over the course of the next several years, from 2001 to 2007, HSIA completed and submitted two studies to the Agency: a developmental toxicity and an immunotoxicity study *via* the inhalation route in rats. These two studies had been planned to be extrapolated to the human oral route using PBPK modeling. In addition, HSIA had planned to fulfill the data need for neurotoxicity *via* the oral route using PBPK modeling of existing published data from the inhalation route. Also, HSIA had planned to conduct a developmental neurotoxicity study in rats *via* the oral route. HSIA did not fulfill its MOU for these four planned studies due to several factors, including problems securing an appropriate lab, discontinuation of a strain of rat previously used in their completed studies, and discrepancies with ATSDR regarding the completeness of the three aforementioned studies using PBPK modeling.

Since 2008, no further action has been taken by OPPT with regards to TCE and its existing data gaps identified by ATSDR.

Appendix B: 2006 Inventory Update Rule Data for TCE

The 2006 Chemical Data Reporting, or CDR, records indicate TCE production volume (PV) to be 100 to 500 Mlbs. Since all importers and manufacturers are not required to report, CDR data likely underestimates actual TCE PV. For the purposes of this draft assessment, the low end of TCE PV was taken to be 100 Mlbs/yr while the high end was taken to be 500 Mlbs/yr.

The data tables below were taken from (US EPA, 2006b).

Table B-1. US EPA 2006 IUR Data for TCE.

Company and Site Information							
Company	**Site**	**City**	**State**	**Zip Code**	**Manufacture**	**Import**	**Site Limited**
Basic Chemicals Company, LLC	Basic Chemicals Co – Wichita Plant	Wichita	KS	67215	Yes	No	No
Chemcentral Corporation	Chemcentral International	Pompano Beach	FL	33069	No	Yes	N/A
Ineos Chlor Americas, Inc.	Ineos Chlor Americas, Inc.	Wilmington	DE	19810	No	Yes	N/A
JSL Chemical Corporation	JSL Chemical Corporation	Palm Beach	FL	33480	No	Yes	N/A
Oxy Vinyl, LP	Oxy Vinyls – LaPorte	La Porte	TX	77571	Yes	No	Yes
PPG Industries, Inc.	PPG Industries – Lake Charles	Lake Charles	LA	70602	Yes	No	No
TR International, Incorporated	TR International Inc – Seattle	Seattle	WA	98101	No	Yes	N/A
The Dow Chemical Company	Dow Chemical – Freeport, TX	Freeport	TX	77541	Yes	No	No

Table B-2. National Chemical Information.

Production volume (aggregated)	100-<500 million lbs
Maximum concentration (at manufacture or import site)	>90%
Physical forms(s)	Liquid
Number of manufacturing, processing, and use sites (aggregated)	≥1,000
Number of reasonably likely to be exposed industrial manufacturing, processing, and use workers (aggregated)	≥1,000
Was industrial processing or use information reported?	Yes
Was commercial or consumer use information reported?	Yes

Table B-3. Summary of TCE Uses.

Type of Processing	Industrial Sector (Based on NAICS)	Industrial Function
Not readily obtainable (NRO)	NRO	NRO
Processing as a reactant	CBI	Intermediates
Processing as a reactant	Industrial gas manufacturing	Intermediates
Processing as a reactant	Other basic organic chemical manufacturing	Intermediates
Processing as a reactant	Other basic organic chemical manufacturing	Other
Processing; incorporation into formulation, mixture, or reaction product	All other chemical product and preparation manufacturing	Solvents (that become part of product formulation or mixture)
Processing; incorporation into formulation, mixture, or reaction product	Invalid data provided	Adhesives and binding agents
Processing; incorporation into formulation, mixture, or reaction product	Machine shops	Solvents (for cleaning or degreasing)
Processing; incorporation into formulation, mixture, or reaction product	Paint and coating manufacturing	Solvents (that become part of product formulation or mixture)
Processing; repackaging	Other basic organic chemical manufacturing	Other
Processing; repackaging	Other chemical and allied products merchant wholesalers	Solvents (for cleaning or degreasing)

Table B-4. TCE Use Category Summary.

Commercial/Consumer Product Category	Maximum Concentration in Related Consumer/Commercial Product Category	Intended for Use in Children's Products in Related Product Category
Adhesives and sealants	>90%	No
Lubricants, greases, and fuel additives	>90%	No
Paints and coatings	1-30%	No
Other	>90%	No
NRO	NRO	NRO

Appendix C: NAICS Codes for TCE Degreasing

An analysis of the North American Industry Classification System (NAICS) identified 78 different industries (NAICS codes are listed in Table C-1).

Table C-1. TCE Used as a Degreaser Primarily in These Industries (US Census, 2008).

NAICS Codes				
33121	331210	332811	334413	336411
33272	331419	332812	334414	336413
33341	331421	332813	334417	336414
33422	332111	332912	334419	336510
33512	332112	332913	334513	337125
33531	332116	332919	334515	337127
33634	332117	332994	335121	339114
33641	332211	332996	335211	339992
33999	332212	332999	335312	339995
314999	332311	333132	335313	339999
321113	332313	333298	335911	488111
323116	332431	333311	335921	493110
325188	332510	333415	335929	811310
325998	332618	333921	335999	928110
326299	332721	333994	336321	
331111	332722	333999	336340	

Each number listed is a different industry that may be associated with TCE/degreasing operations. Those interested may go to the following URL and type in a code - http://www.census.gov/eos/www/naics/ (US Census, 2008)). For example, the following results are seen when the listed numbers are searched:

33121:

33121 Iron and Steel Pipe and Tube Manufacturing from Purchased Steel[T]

331210 Iron and Steel Pipe and Tube Manufacturing from Purchased Steel

332811 (results below slightly edited for simplicity)

Metal Heat Treating - This U.S. industry comprises establishments primarily engaged in heat treating, such as annealing, tempering, and brazing, and cryogenically treating metals and metal products for the trade.

Establishments primarily engaged in both fabricating and heat treating metal products are classified in the Manufacturing sector according to the product made.

Annealing metals and metal products for the trade

Brazing (i.e., hardening) metals and metal products for the trade

Burning metals and metal products for the trade

Cold treating metals for the trade

Cryogenic treating metals for the trade

Hardening (i.e., heat treating) metals and metal products for the trade

Heat treating metals and metal products for the trade

Shot peening metal and metal products for the trade

Tempering metals and metal products for the trade

Appendix D: Calculations for Small Commercial Worker Degreaser Exposures

In Figure E-1, a solvent degreasing facility is partitioned into two zones: the near-field and the far-field (Keil *et al.*, 2009). This is done because in occupational settings, contaminant levels in the near-field are considered to provide a better representation of a worker's personal breathing zone than those in the far-field; potential worker exposures depend on how close a worker is to the emission source. Also, for this risk assessment, the far-field exposures will represent bystanders, or non-users. In other words, those individuals who are in the building (and perhaps even the room), but are not physically close to the volatile source as shown in Figure D-1.

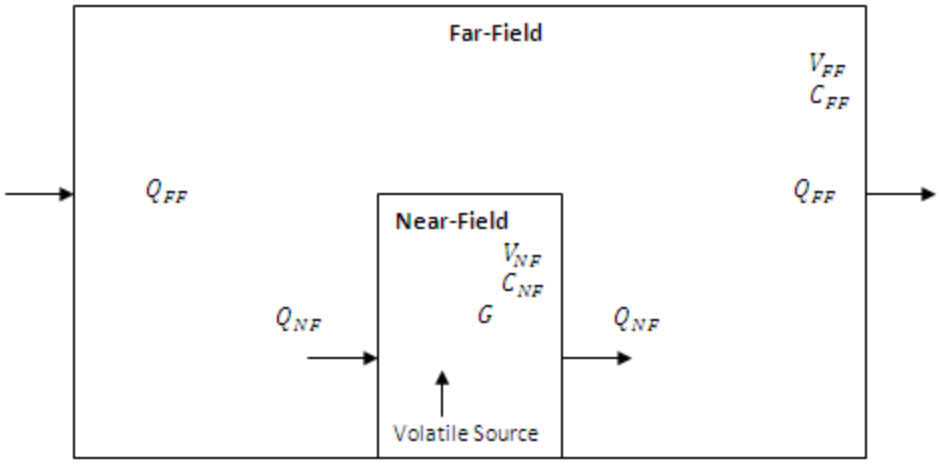


Figure D-1. An Illustration of an Imperfectly Mixed Room; Near-Field/Far-Field Approximation of a Solvent Cleaning Facility; Potential Worker Exposures Depend on How Close a Worker is to the Emission (Volatile) Source.

Near-Field Mass Balance

$$V_{NF}\frac{dC_{NF}}{dt} = C_{FF}Q_{NF} - C_{NF}Q_{NF} + G \quad [1]$$

Far-Field Mass Balance

$$V_{FF}\frac{dC_{FF}}{dt} = C_{NF}Q_{NF} - C_{FF}Q_{NF} - C_{FF}Q_{FF} \qquad [2]$$

Where:

V_{NF} = near-field volume
V_{FF} = far-field volume
Q_{NF} = near-field ventilation rate
Q_{FF} = far-field ventilation rate
C_{NF} = average near-field concentration
C_{FF} = average far-field concentration
G = average generation rate

At steady-state, Equations 1 and 2 can be reduced to the following:

$$C_{NF} = \frac{G}{Q_{NF}\left(1 - \frac{Q_{NF}}{Q_{NF}+Q_{FF}}\right)} \qquad [3]$$

$$C_{FF} = \frac{C_{NF}Q_{NF}}{Q_{NF}+Q_{FF}} \qquad [4]$$

For the purposes of mass transfer from and to the near-field, the free surface area, is defined to be the surface area that is available for mass transfer; the , will not necessarily be equal to the surface area of the near-field. For instance, if the near-field is defined to be a rectangular region, as illustrated in Figure D-1, the near-field floor will not be available for mass transfer; thus, the , will be less than the actual surface area of the near-field:

$$FSA = 2(L_{NF} * H_{NF}) + 2(W_{NF} * H_{NF}) + (L_{NF} * W_{NF}) \qquad [5]$$

Where: L_{NF}, W_{NF}, H_{NF} are the length, width, and height of the near-field, respectively.

If the near-field indoor wind speed, v_{NF} is known and the area for mass transfer into and from the near-field is equal, then the Near-Field ventilation rate, Q_{NF}, is given by:

$$Q_{NF} = \frac{1}{2} * FSA * v_{NF} \qquad [6]$$

Based on the model inputs in Table D-1, potential workplace TCE inhalation exposure values can be estimated for workers in the near-field and for non-users in the far-field (see Table D-2). The majority of data regarding worker exposure to TCE was obtained from degreasing operations; the data indicated that exposure is likely to vary, although mean TWA concentrations were generally consistent and usually ranged from ≤50 to 100 ppm (ATSDR, 1997). This is similar to the exposure values presented in the EU Risk Assessment for TCE (EC, 2004). The "typical" exposure values in Table D-2 are also similar, being of the same order of magnitude.

Table D-1. Near-Field/Far-Field Model Inputs.

Parameter	Units	Parameter Values	Comments
		Small Industrial/ Commercial Facilities	
Q_{FF}	ft^3/minute	500 (worst case) 3,000 (typical)	US EPA (1991)
V_{NF}	cm/second	10	~50th percentile; Baldwin and Maynard (1998)
L_{NF}	ft	10	Assumes volatile source is centered in the fear-field and worker activities are within 5 feet of the emitting source
W_{NF}	ft	10	
H_{NF}	ft	6	Adequate height to capture a typical worker's breathing zone
FSA	ft^2	180	Equation (5)
G	g/minute	16.73	No local exhaust ventilation (LEV); see Table 3-7 in main body of this report.
G	g/minute	1.67	With LEV; potential operating TCE emissions reduced by 90%; Wadden *et al.* (1989)

Results of the calculations are shown below in Table E-2.

Table D-2. Potential Workplace TCE Inhalation Exposures and Number of Workers Exposed; No LEV.

Type of Facility	Potential Workplace TCE Inhalation Exposures (8-hour TWA)					
	Near-Field			Far-Field		
	Typical (ppm)	Worst Case (ppm)	Number of Workers	Typical (ppm)	Worst Case (ppm)	Number of Workers
Small industrial/ commercial	17	63	7,415	9	55	17,796

The potential workplace inhalation exposures in Table D-2 do not take LEV into account. Engineering controls, such as LEV, are recommended if practical (Arkema, 2011). The use of LEV can reduce potential operating TCE emissions into the workplace by approximately

90 percent (Wadden *et al.*, 1989). Based on the model inputs in Table D-1, potential workplace TCE exposures in the presence of LEV are presented in Table D-3.

Table D-3. Potential Workplace TCE Inhalation Exposures and Number of Workers Exposed; With LEV.

Type of Facility	Potential Workplace TCE Inhalation Exposures (8-hour TWA)					
	Near-Field			Far-Field		
	Typical (ppm)	Worst Case (ppm)	Number of Workers	Typical (ppm)	Worst Case (ppm)	Number of Workers
Small industrial/ commercial	2	6	7,415	1	5	17,796

Appendix E: Converting E-FAST ADRs to Concentration in Air

The exposure values generated using the E-FAST/CEM models are in mg/kg-bw/day (notes 10 and 11). The only output in the acute exposure scenario expressed as a concentration is the peak concentration, which represents the maximum concentration in air calculated by the model during any 10-second time step during (in this case) 24 hours. This value is not a realistic one to use, even as a worst-case scenario (all peak concentrations can be found in documents cited in notes 10 and 11).

Thus, to convert the E-FAST CEM outputs from mg/kg-bw/day to ppm, the following methodology was used: using the equation from the E-FAST manual to calculate the ADR (acute dose rate).

The general expression for the potential acute dose rate (ADR_{pot}) is as follows:

$$ADRpot = \frac{(Cair \times InhR \times FQ \times DEv \times ED)}{BW \times AT}$$

where:

ADR_{pot} = potential acute dose rate (mg/kg-bw/day)
Cair = exposure concentration (mg/m^3)
InhR = inhalation rate (m^3/hour)
FQ = frequency of product use (events/year)
DEv = duration of an event (hour/event)
ED = exposure duration (years of product usage)
BW = body weight (kg)
AT = averaging time (days)

Rearranging and simplifying this equation to calculate *an approximation* for C_{air} over the 24-hour averaging time for the ADR_{POT} results in the following equation:

$$Cair \approx \frac{ADRpot \times BW}{InhR \times 24}$$

This simplification is reasonable since the averaging time for acute exposure is one day (24 hours). In both scenarios, the frequency is just once per day. Although the duration of the event for the two consumer scenarios is either one hour (degreaser) or 0.5 hours (clear protective coating spray)[26], for the purposes of this exercise and to convert the model output to

[26] However, for the user in both scenarios, the inhalation rates were slightly higher during use of the product, as stipulated in the model outputs. Thus, for the degreaser use, an inhalation rate of 0.74 m^3/hour (for 21 to 78 year olds, 0.72 m^3/hour for the 16 to 20 year olds) was used for one hour, and 0.611 m^3/hour (for 21 to 78 yr olds, 0.679 m^3/hour for the 16 to 20 yr olds) for the remaining 23 hours. For the clear protective coating spray use, the

a more useable exposure value to compare to the hazard value, there is no correction for this difference. This assumption is still conservative since the values generated are reasonably high exposures that probably overestimate the actual exposures.

This is borne out by comparing the values calculated for the hobbyist degreaser scenarios (2 ppm for the 16 to 20 year olds and the 21 to 78 year olds) to the estimate for the small commercial operators in which the typical and worst-case values of 2 and 6 ppm, respectively, were estimated for the local exhaust ventilation (LEV) scenario (the same values without LEV were 17 and 63 ppm, respectively).

An example calculation is presented below, since the final value is in mg/m^3 and the desired units will be in ppm. All calculated values are presented in Table E-1.

For the clear protective coating spray use, 21- to 78-yr-old user:

ADR_{pot} = 0.45 mg/kg-bw/day
InhR (during use; 0.5 hours) = 0.74 m^3/hour
InhR (other times; 23.5 hours) = 0.611 m^3/hour
BW = 80 kg (using 2011 Exposure Factors Handbook, US EPA, 2011d)

C_{air} = (0.45)(80)/[0.74 x 0.5) + [0.611 x 23.5) = 2.4 mg/m^3; converting to ppm[27] = 0.446 ppm (converted to 0.4 ppm to use a single significant figure given the assumptions in the back-calculation).

Table E-1. Estimated TCE Inhalation Calculated Concentration in Air (Over Course of Day) from Use of Two Hobbyist Products Indoors at Residences.

Ages	Clear Protective Coating Spray User ADR_{pot} (ppm)	Clear Protective Coating Spray Non-user ADR_{pot} (ppm)	Solvent Degreaser User ADR_{pot} (ppm)	Solvent Degreaser Non-user ADR_{pot} (ppm)
<1	NA	0.1	NA	0.8
1-2	NA	0.1	NA	0.8
3-5	NA	0.1	NA	0.8
6-10	NA	0.1	NA	0.8
11-15	NA	0.1	NA	0.8
16-20	0.4	0.1	2	0.8
>21	0.4	0.1	2	0.8

higher, user inhalation rate was used for 0.5 hours, with the "normal" rate used for 23.5 hours. This correction was not done for any bystander (non-user) scenario.

[27] ppm = mg/m^3/5.374.

Appendix F: Hazard Values Identified for use in this Risk Assessment

Table F-1. Studies Identified In US EPA (2011c) For Use In Dose-Response Assessment For TCE.

Target Organ	Species	Route of Exposure[a]	Range of Doses or Concentrations[b]	Duration	POD Type[c]	Effect	HEC_{50} (ppm)	HEC_{99} (ppm)	Reference
Liver	Mouse	Inhalation	37-3,600 ppm	30-120 days	BMDL = 21.6 ppm	Increased liver weight/body weight ratio	25	9.1	1
	Rat	Inhalation	100-1,000 ppm	28 days	BMDL = 25 ppm		53	19	2
	Mouse	Oral (g)	100-3,200 mg/kg-bw/day	6 weeks	BMDL = 82 mg/kg-bw/day		32	11	3
Kidney	Rat	Inhalation	100-600 ppm	104 weeks	BMDL = 40.2 ppm	Pathology changes in renal tubule	0.28	0.038	4
	Mouse	Oral (g)	869-2,339[d] mg/kg-bw/day	90 weeks	LOAEL = 620 mg/kg-bw/day		3.9	0.5	5
	Rat	Oral (g)	500-1,000 mg/kg-bw/day	104 weeks	BMDL = 9.45 mg/kg-bw/day		0.042	0.0056	6
	Mouse	Inhalation	37-3,600 ppm	30-120 days	BMDL = 34.7 ppm	Increased kidney weight/body weight ratio	0.88	0.12	1
	Rat	Inhalation	100-1,000 ppm	28 days	BMDL = 15.7 ppm		0.099	0.013	2
Neuro-toxicity	Human	Inhalation	Mean exposure of CxT	Mean of 16 years	LOAEL = 14 ppm	Trigeminal nerve effects	14	5.3	7
	Rat	Oral (drw)	25-47 mg/kg-bw/day	8 weeks	LOAEL = 47 mg/kg-bw/day	Demyelination of hippocampus	18	7.1	8
	Rat	Inhalation	50-300 ppm	6 weeks	LOAEL = 12 ppm	Changes in wakefulness	13	4.8	9
	Rat	Oral (g)	1,000 mg/kg-bw/day	6 weeks	LOAEL = 710 mg/kg-bw/day	Loss of neurons	126	47	10
	Rat	Inhalation	300 ppm	24 days	LOAEL = 300 ppm	Decreased regeneration of sciatic nerve	274	93	11
	Mouse	Inhalation	150-300 ppm	24 days	LOAEL = 150 ppm		378	120	

Table F-1. Studies Identified In US EPA (2011c) For Use In Dose-Response Assessment For TCE.

Target Organ	Species	Route of Exposure[a]	Range of Doses or Concentrations[b]	Duration	POD Type[c]	Effect	HEC_{50} (ppm)	HEC_{99} (ppm)	Reference
Immuno-toxicity	Mouse	Oral (drw)	1.4-14 ppm	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Decreased thymus weight	0.092	0.033	12
	Mouse	Oral (drw)	1.4-14 ppm	27-30 weeks	LOAEL = 0.35 mg/kg-bw/day	Increased anti-dsDNA	0.092	0.033	12
	Mouse (auto-immune prone strain)	Inhalation	500-2,000 ppm	8 weeks	LOAEL = 70 ppm	Changes in immunoreactive organs	97	37	13
	Mouse	Oral (drw)	0.1-5.0 mg/mL	4 or 6 months	LOAEL = 18 mg/kg-bw/day	Immunosuppression	4.8	1.7	14
	Rat	Inhalation	100-1,000 ppm	28 days	BMDL = 24.9 ppm	Immunosuppression	29	11	2
Reproduct-ive toxicity	Human (male)	Inhalation	Mean exposure = 29.6 ppm	Measured values after an 8-hour work shift; mean years on job was 5.1	BMDL = 1.4 ppm	Sperm effects	1.4	0.5	15
	Mouse (male)	Inhalation	1,000 ppm	6 weeks	LOAEL = 180 ppm	Sperm effects	190	67	16
	Rat (male)	Inhalation	376 ppm	2-10 weeks, 12 weeks, 24 weeks	LOAEL = 45 ppm	Sperm effects and male reproductive tract effects	32	13	17
	Mouse (male)	Inhalation	1,000 ppm	19 days over 4 weeks, 1-4 weeks	LOAEL = 180 ppm	Effects on epididymis epithelium	190	67	18
	Rat (male)	Oral (drw)	143-270 mg/kg-bw/day	14 days	LOAEL = 141 mg/kg-bw/day	Decreased *in vitro* fertilization	16	9.3	19
	Rat (fem)	Oral (g)	475-1,125 mg/kg-bw/day	9 days (during gestation)	LOAEL = 475 mg/kg-bw/day	Delayed parturition	98	37	20
	Rat (both sexes)	Oral (f)	72-389 mg/kg-bw/day	18 weeks	LOAEL = 389 mg/kg-bw/day	Decreased mating (both sexes exposed)	204	71	21

Table F-1. Studies Identified In US EPA (2011c) For Use In Dose-Response Assessment For TCE.

Target Organ	Species	Route of Exposure[a]	Range of Doses or Concentrations[b]	Duration	POD Type[c]	Effect	HEC_{50} (ppm)	HEC_{99} (ppm)	Reference
Develop-mental toxicity	Rat (female)	Inhalation	100 ppm	13 days (during gestation)	LOAEL =17 ppm	Increased resorptions	16	6.2	22
	Rat (female)	Oral (g)	475-1,125 mg/kg-bw/day	9 days (during gestation)	BMDL = 32.2 mg/kg-bw/day	Increased resorptions	29	28	20
	Rat (female)	Inhalation	100 ppm	13 days (during gestation)	LOAEL = 17 ppm	Decreased fetal weight	16	6.2	22
	Rat (female)	Oral (drw)	0.0025-1,100 ppm	22 days (throughout gestation)	BMDL = 0.0207 mg/kg-bw/day	Heart malformations	0.012	0.0037	23
	Rat (male pups)	Oral (g)	50 and 290 mg/kg-bw/day	PNDs 10-16	LOAEL = 50 mg/kg-bw/day	Decreased rearing activity	8	3	24
	Rat (female)	Oral (drw)	312-1,250 mg/L	From gestation through 21 days post-partum	LOAEL = 45 mg/kg-bw/day	Increased exploratory behavior in male pups	22	8.4	25

[a]g = gavage, drw = drinking water, f = feed

[b]Controls (or zero dose/concentration) are not presented, so a sense of the lowest and highest values is understood.

[c]POD type can be NOAEL, LOAEL, or BMDL; the IRIS program adjusted all values to continuous exposure.

[d]Reported doses were TWAs on the days in which animals received a dose (66 weeks over the 90-week period).

Reference List (all as cited in US EPA, 2011c):

1 = Kjellstrand *et al.* (1983)
2 = Woolhiser *et al.* (2006)
3 = Buben and O'Flaherty (1985)
4 = Maltoni and Cotti (1986)
5 = NCI (1976)
6 = NTP (1988)
7 = Ruijten *et al.* (1991)
8 = Isaacson *et al.* (1990)
9 = Arito *et al.* (1994)
10 = Gash *et al.* (2008)
11 = Kjellstrand *et al.* (1987)
12 = Keil *et al.* (2009)
13 = Kaneko *et al.* (2000)
14 = Sanders *et al.* (1982)
15 = Chia *et al.* (1996)
16 = Xu *et al.* (2004)
17 = Kumar *et al.* (2000); Kumar *et al.* (2001)
18 = Forkert *et al.* (2002); Kan *et al.* (2007)
19 = DuTeaux *et al.* (2004)
20 = Narotsky *et al.* (1995)
21 = NTP (1986)
22 = Healy *et al.* (1982)
23 = Johnson *et al.* (2003)
24 = Fredriksson *et al.* (1993)
25 = Taylor *et al.* (1985)